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Original Articles

IMMUNITY AGAINST H-SUBSTANCE

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A GREAT deal of evidence exists to support the hypotheses of Dale and Laidlaw[1] and Lewis[2] that the symptomatology of clinical allergies is due to an antigen-antibody combination which results in the production of H-substance. The major activity of this H-substance is indistinguishable from that of histamine.

Whether the action of H-substance is due to histamine alone or to other additional factors, the work of Dragstedt,[3] Katz,[4] Katz and Cohen[5] and others demonstrates conclusively that histamine or some substance indistinguishable from it is formed in allergic reactions.

Many attempts have been made to decrease patients' reactivity to histamine by means of histaminase and by the parenteral administration of histamine. While it is true that individual constitutional tolerance to histamine can be increased manyfold following its parenteral administration, there is no evidence that a diminution in the whealing response of the skin to histamine has ever been accomplished by such procedures.

If diminution of the whealing response of the skin to histamine could be produced, it would be possible to study the relationship of histamine to H-substance and the part that each of these plays in producing the allergic reaction.

In 1941, Sheldon, Fell, Johnston, and Howes[6] described the clinical effect of a histamine-azoprotein in allergic disease. This material, a chemical combination of benzylchlor-histamine with despeciated horse globulin, can be injected into animals and man without danger, since it contains no free histamine and does not break down rapidly in the body. The despeciation of the horse globulin makes it possible for the compound to be given to asthmatic patients sensitive to horse serum without reaction.

The expense of this investigation was defrayed in part by a grant from The Parke, Davis, & Co.

Following the report of Sheldon et al., we obtained this material from Dr. Fell and used it in a number of experiments. Our findings in man[7] and those of Fell and his co-workers in lower animals are in agreement. Following the parenteral administration of histamine-azoprotein, precipitins develop which are at least in part specific for the histamine component of the molecule. Immunized animals are protected significantly against anaphylaxis, and sera from treated human beings neutralize histamine in vitro. In addition, an increased local tolerance to histamine as evidenced by a diminution in the whealing response of the skin was noted in some of the treated human beings.

These findings encouraged us to continue these studies as follows:

METHOD

Serial dilutions of histamine were prepared from tablets containing 1 mg. of histamine base. The dilutions ranged in multiples of 2, from 1:200,000 through 1:6,400,000. Solutions were used within 4 hours of their preparation. Tests were made on the inner surface of the forearm by the iontophoretic technique, using 1 sq. cm. pieces of filter paper, a 1 sq. cm. positive electrode, and 1 Ma. of direct current for 3 minutes. A control test with physiologic saline was used at the highest and more sensitive portion of the test area. Each subsequent histamine dilution was tested at a site 1½ inches below the previous test area. That dilution of histamine which produced definite punctate whealing in the test area was considered to be the threshold for the person being studied, provided there was no reaction in the control area.

RESULTS WITH HISTAMINE

Fifty nonallergic persons were used to determine the normal skin threshold to histamine. In 45 the initial reaction occurred with a dilution of 1:6,400,000; and in 5 with a dilution of 1:3,200,000.

A series of patients with urticaria, allergic rhinitis, and intrinsic asthma were treated with histamine-azoprotein. The doses were given subcutaneously at 3- to 7-day intervals. The initial dose was 0.10 c.c. Subsequent doses were 0.5, 0.75, 1.0 c.c., the increases being determined by the amount of local irritation produced by the previous dose. An attempt was made to give at least 5 c.c. within a period of 30 days. Some patients were continued on weekly treatments for several months and received a total of 30 c.c. Others were given an initial course of treatment; then a rest period of 8 to 16 weeks followed by a second course. Studies of the skin test thresholds to histamine were determined at intervals during the treatment and after treatment had been discontinued. Initial threshold studies were made in certain of the patients.

The result of these experiments in 10 well-treated cases are shown in Table I.

TABLE I

HISTAMINE THRESHOLD IN CASES TREATED WITH HISTAMINE AZOPROTEIN

CASE NO.	THRESHOLD
1	200,000
2	800,000
3	1,600,000
4	400,000
5	1,600,000
6	6,400,000
7	400,000
8	1,600,000
9	800,000
10	6,400,000

Fifty Normals
45 at 6,400,000
5 at 3,200,000
C. R. 5.25

It will be noted that in 2 cases, the whealing threshold was within normal limits. In 8, it varied between 1:200,000 and 1:1,600,000; this represents a reduction of 4 to 32 multiples in reactivity.

Statistical comparison of these findings with those in normals gives a critical ratio of 5.25. This ratio leaves no doubt of the significance of these differences since the odds in favor of significance are many thousand to one.

It may be concluded, therefore, that immunization with histamine azoprotein protects the skin against histamine *introduced locally*. It does not follow, however, that such treatment would protect against histamine, H-substance, or both, as they are produced in the local site as the result of allergic reaction.

The work of Alexander[8] has demonstrated that the wheal produced by eserine resembles in all respects that which occurs in allergic reactions. We, therefore, studied eserine wheals in nonallergic persons and in persons treated with histamine-azoprotein.

METHOD

Serial dilutions of eserine sulfate ranging from 1:100 to 1:1000 were tested on the skin by the iontophoretic method described.

TABLE II

ESERINE THRESHOLD IN CASES TREATED WITH HISTAMINE AZOPROTEIN

CASE NO.	THRESHOLD
1	800
6	800
7	200
8	800
9	1000
10	100
11	400
12	1000
13	1000

Fifteen Normals
13 at 1000
2 at 800
C R. 2.89

Fifteen normals were used to determine the eserine threshold. Of these, 13 reacted at 1:1000 dilutions, 2 at 1:800. Of nine treated cases, 2 reacted at 1:1000; 6 required stronger concentrations. (Table II.)

Statistical comparison of these results gave a critical ratio of 2.89, the odds in favor of significance being about a hundred to one.

We conclude from these experiments that treatment with histamine azoprotein protects against H-substance released by eserine stimulation. Since both the eserine wheal and the allergic wheal are mediated by an H-substance mechanism, we see no reason to doubt that there would also be protection against the H-substance released in an allergic reaction.

REFERENCES

1. Dale, H. H., and Laidlaw, P. P.: The Physiological Action of B-Iminazolylethylamine, J. Physiol. **41**: 318, 1910.
2. Lewis, T., and Grant, R. T.: Vascular Reactions of the Skin to Injury (Part II: The Liberation of a Histamine-like Substance in Injured Skin; the Underlying Cause of Factitious Urticaria and of Wheals Produced by Burning; and Observations Upon the Nervous Control of Certain Skin Reactions), Heart **11**: 209, 1924.
3. Dragstedt, C. A.: Anaphylaxis and Allergy, Ann. Int. Med. **13**: 248, 1939.
4. Katz, G.: Histamine Release in the Allergic Skin Reaction, Proc. Soc. Exper. Biol. & Med. **49**: 272, 1942.
5. Katz, G., and Cohen, S.: Experimental Evidence for Histamine Release in Allergy, J. A. M. A. **117**: 1782, 1941.
6. Sheldon, J. M., Fell, N., Johnston, J. H., Howes, H. A.: A Clinical Study of Histamine Azoprotein in Allergic Disease (A Preliminary Report), J. ALLERGY **13**: 18, 1941.
7. Cohen, M. B., and Friedman, H. J.: Antibodies to Histamine Induced in Human Beings by Histamine Conjugates, J. ALLERGY **14**: 195, 1943.
8. Alexander, H. L.: Allergic Syndromes in the Absence of Allergens, J. ALLERGY **11**: 163, 1940.

DEATHS FROM ASTHMA

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IN OCTOBER, 1941, Dr. Tracy B. Mallory and I demonstrated a chart at the annual meeting of the American Clinical and Climatological Association. Much of the material in the present communication was presented at that time and was recorded in the Transactions of that Association, but the circulation of the Transactions is small and since the chart appears to be of some importance, it is reprinted here. (See Chart 1.)

In December, 1941, Dr. Mallory gave a special lecture before the American Society for the Study of Asthma and Allied Conditions, and he demonstrated this same chart. He pointed out that deaths from asthma itself were caused by suffocation due to the formation of tough, sticky plugs which filled most of the smaller bronchi and occluded them. A description of the details of the pathology in these cases will be reported later by Dr. Mallory.

Chart 1 shows fifty patients in whom asthma was the obvious symptom and who died and came to autopsy at the Massachusetts General Hospital. Most of these patients died not only with asthma but because of asthma.

The pathology is typical. The lungs were blown up and were markedly distended. On removal from the body they did not collapse, but formed a cast of the chest cavity. They had a pale gray appearance with a fine bluish mottling, which was uniform throughout. In the cut section one could almost see the dilated air spaces, but more important were the bronchi. The cut ends were prominent and stood out quite sharply against the background. In most of them the lumen was filled with a tough sticky material which partially occluded it. This mucus acted as a ball valve to trap the inspired air and so to increase the emphysema, and this process continued until the air could hardly get in at all, with the patient dying of suffocation.

Under the microscope plugs could be seen in most of the smaller bronchi. The bronchial wall was thickened to some extent, and in the wall the mucous glands seemed to be increased both in size and in number so that we have considered the theory that the primary lesion was a disturbance in the activity of these glands; that for some reason they worked overtime to produce mucus in quantity and mucus of a rather special, sticky tough type.

Chart 1 shows the duration of asthma and the mode of death. It is interesting to compare this with the clinical diagnosis.

Cases 1 to 7 all had asthma of the extrinsic type. The age of onset was early. The attacks did bear a relation to changes in environment. Skin tests were usually positive. In these cases, however, death was

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caused not by asthma, but by some other condition. Four of these seven patients died of pneumonia, one at the age of 18; the others were in their forties. With the pneumonia in two cases was a *cor pulmonale*. In two other cases this *cor pulmonale* was the only important finding at autopsy. In Case 2 the story was of long-standing asthma which in early life had been relieved in Colorado, but which had been continuous since the age of 41. Death occurred at the age of 55 from arteriosclerotic heart disease with coronary involvement.

Cases 8, 9, 11, 12, and 13 are of particular interest. Here was a group of young people whose trouble began about the age of 20, at first as a chronic vasomotor rhinitis. Soon, however, asthma came, and this asthma increased steadily in its severity until death from asthma itself occurred at or before the age of 30 in four cases and at the age of 37 in the fifth case. In three of these five cases, periarteritis nodosa was a complication, and the fact is of considerable theoretical interest. In none of the five cases was it possible to show that foreign substances in food or dust had any relation to the cause of their trouble. Oxygen tents and a diet of liquids without milk excluded the factors of dust and diet, but they had no effect here. Clinical allergy in the extrinsic sense could be ruled out.

Four of the next six patients (Cases 14 to 19) died of intercurrent disease. Three had pneumonia, and one, coronary disease. In the other two, *cor pulmonale* was considered to be the important cause of death, and it is proper to assume that the final dilatation of the right ventricle was caused by the long-standing and severe asthma.

The last 28 cases are of special interest. Here is asthma beginning suddenly between the ages of 40 and 50. Death was due not to pneumonia or to heart disease but to asthma itself. In most cases the disease was continuous and progressive after onset, but the life line is broken by dashes representing the attacks; and then death came often quite suddenly in an attack which was more severe than the others and in which the formation of sticky plugs was extensive enough to shut off all breathing.

In several of these cases, the total course of the disease was remarkably short, two years, three years, or maybe five years, but sometimes only a few months intervened between the first sign of asthma and death during a typical asthmatic paroxysm, with typical findings at autopsy. This is a serious disease. What causes it, however, is a question which is still unanswered. What happens when the active businessman who appears healthy in every way suddenly develops asthma at about the age of 50 and then continues to cough and wheeze more and more until in a few years he chokes to death? It is not a pleasant prospect, but evidently it can happen.

How often does this happen? How many cases are there in the two groups younger and older, and what numerical relation do they bear to all the other types and kinds of asthma? Figures on this are not yet available, but it is hoped that they can be presented soon.

Theories about this group of cases are numerous; no one of them is really satisfactory. The first one is: Is this allergy after all? We have tried hard to correlate the onset and the course of the disease with changes in environment and changes in diet, but with no success. From the practical point of view, allergy can be excluded, at least so far as foods and dusts are concerned.

Allergy to drugs is a possibility. Some of these patients were sensitive to aspirin, and the fact always implies a severe type of asthma. To one of them (Case 24), the nurse gave a 5 grain tablet of aspirin one day, and within ten minutes his asthma became of maximum severity with deep cyanosis and with almost absent breath sounds in his chest. He almost died, but after prompt treatment with epinephrine and oxygen, he rallied and survived. Case 48 is interesting. This woman of

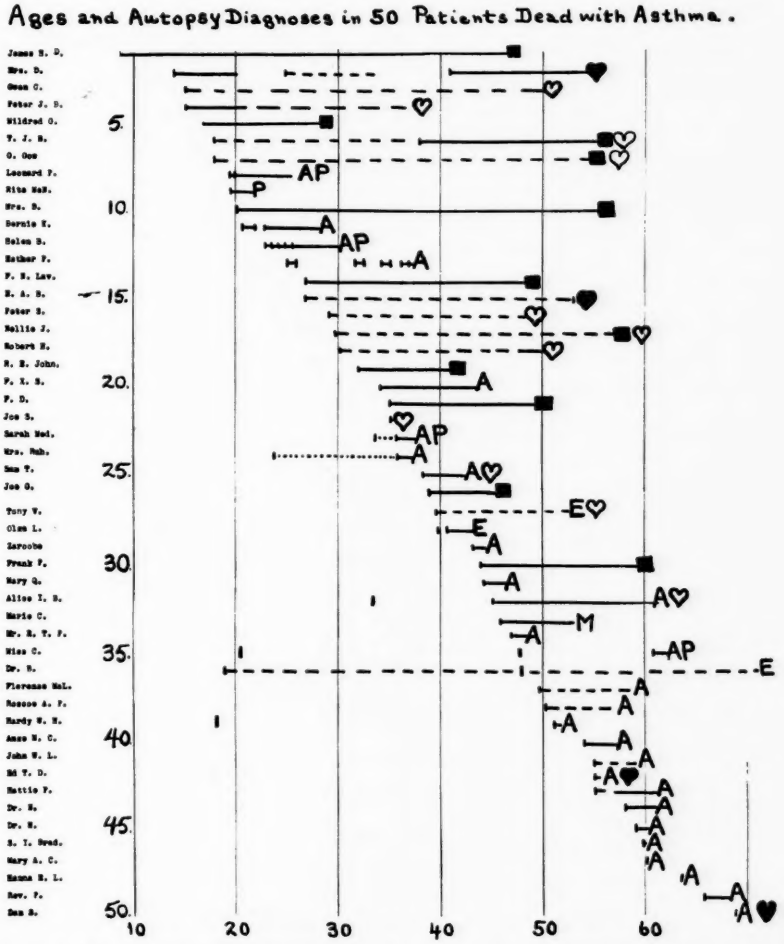

Chart 1.—The ages and autopsy diagnoses in fifty patients dead with asthma. Each horizontal line begins at the age of onset of asthma and ends at the age of death. Age figures are at the bottom. Solid lines represent continuous persistent asthma. Breaks in the line indicate that asthma occurred in attacks. Dots indicate chronic vasomotor rhinitis before the onset of asthma. The cause of death is shown by symbols: *Squares*, pneumonia; *solid heart*, intercurrent heart disease; *open hearts*, cor pulmonale; *P*, periarteritis nodosa; *E*, emphysema (structural); *M*, meningitis; and *A*, asthma.

63 had had hay fever in childhood, but no symptoms after her twenties. Three weeks before admission, she developed a bad cold and then suddenly had asthma of considerable severity. Adrenalin relieved her and was given several times. She improved in a week or so and for nine days remained quite comfortable. Suddenly, however, the asthma came on her again. She was given pantopon by the family physician and pantopon again on arrival at the hospital. She died in 48 hours with the typical pathology of asthma. Morphine is a dangerous drug to use in severe asthma. Several of the patients in the older group died in the Emergency Ward within a few hours; sometimes within a few minutes of their admission to the hospital. In each case they were given morphine. One wonders, although one can prove nothing.

Could this "intrinsic" asthma be the expression of a bacterial allergy with a sensitization from a chronic focal infection? Some patients have been improved when their sinuses were drained, and a larger number derived greater benefit from the extraction of bad teeth. Cultures and autogenous vaccines have been made, and skin tests with the vaccines have been applied in the hope of finding immediate urticarial reactions comparable to those produced with pollen extracts. In one or two cases immediate reactions have been found, but it was only in one or two, and on the whole all efforts to prove a true bacterial allergy have been found wanting. Quite often one observes a delayed inflammatory reaction of the tuberculin type, but this may and often does refer to the past history and may have little to do with the present illness.

A nerve reflex from the nose or sinuses has been suggested. Weille[3] believes it possible that there may be a sort of perverted reflex between nose and chest, but the theory cannot yet be proved.

Endocrine disturbances must be thought of, at least in passing; and food (vitamin) deficiencies must also be included, if only because of the variations found in the sensitization of guinea pigs which are fed on different fodders. (Sulzberger and Simon.[4])

Much more interesting is the conception that this disease, especially in the older group, is a degenerative process. "Pulmonary fibrosis" and "pulmonary arteriosclerosis" are terms which imply disturbances in lung function due to increased connective tissue in the bronchial wall in the one case and in the blood vessels in the other. It is proper to think of each of these as having an early form and a mild degree of severity, but here too much further study is needed.

"Primary idiopathic emphysema" is another term which implies changes in the alveoli. The letter *E* appears on Chart 1 opposite three cases; in them, the lungs were distended, but the distention was not marked and on the cut surface the typical mucous plugs were not seen. So far the only reasonable way to explain the death in these cases has been to assume that the dilatation of alveoli has lead to the breakdown, "atrophy," of the alveolar walls and the coalescence of many small sacs into larger air spaces, the process interfering more and

more with the transport of gases between air and blood until finally the small amount of lung alveolar surface remaining was no longer sufficient to support life.

Cor-pulmonale, hypertrophy and dilatation of the right heart, was present in twelve cases in this series, and in five it was considered to be the cause of death. Whereas cor-pulmonale has been assumed to depend upon an obstruction to the flow of blood from the right heart, anatomic emphysema as the cause of this obstruction was observed in only two cases. What caused the hypertrophy in the others? The question is pertinent and hard to answer. It is our impression that in severe chronic asthma an obstruction to the pulmonary arterial system can be caused by changes which are functional and not organic. Over-activity of mucous glands makes plugs. Plugs cause emphysema of a functional sort and then the dilatation of alveoli presses on the lung capillaries. Finally, one comes to the consideration of histamine and acetylcholine as chemical effectors capable of causing very serious damage and of acting over a prolonged period of time.

Further study of this group of cases is in progress. It is the tabulation and arrangement of the fifty patients who have come to autopsy; this suggests that within the group labelled so far "intrinsic asthma," there is a subgroup which indicates a disease of considerable uniformity and of considerable severity.

The chart of our own cases (Chart 1) suggests that the typical pathology which we believe to be characteristic of death from asthma, the "A" cases, occurs chiefly in the older age groups. That this conclusion may be a little too hasty is shown by a review of the literature. Also Chart 1 suggests that the type of asthma which begins in childhood, usually the "extrinsic" type, is a different disease from the other type, "intrinsic," which begins later. As a matter of fact, there is nothing in the present paper which contradicts this idea, since it deals with an end result which may develop from a variety of causes and be common to each of them.

Chart 2 is similar to Chart 1, but it is compiled from the autopsied cases recorded in the literature. This chart includes only the "A" cases, and the fact requires a little explanation. The diagnosis of death from asthma depends in part upon the clinical picture of the patient, but it depends more upon the pathology as found at autopsy. In 1926, I[5] studied the cases described by Huber and Koessler,[6] and I ruled out many of them as having died from other causes besides asthma. Now, however, with greater experience, a further study of these old case reports shows that my first impression was too critical. Whereas the clinical courses of several of Huber and Koessler's patients did suggest pneumonia or heart disease, or even tuberculosis, the fact is that the autopsy showed the findings which we have come to recognize as typical of asthma. With this more liberal interpretation, fifteen of the twenty-one cases described by Huber and Koessler can now be identified as having died of asthma and so they can be included here.

The criteria for the cases listed from the literature in Chart 2 have been, first, a clinical story of asthma and a mode of death compatible with that diagnosis; second, an autopsy which showed distended or voluminous lungs with exudate of some viscosity filling most of the middle-sized and small bronchi; and, third, the absence of gross evidence for any other cause of death. On the basis of these criteria, 58 cases have been listed as being "A" cases with death from asthma per se.

Contrary to the impression derived from Chart 1, Chart 2 shows well that death from asthma is not at all limited to older people. Infants have died with the typical picture of bronchi occluded by sticky plugs

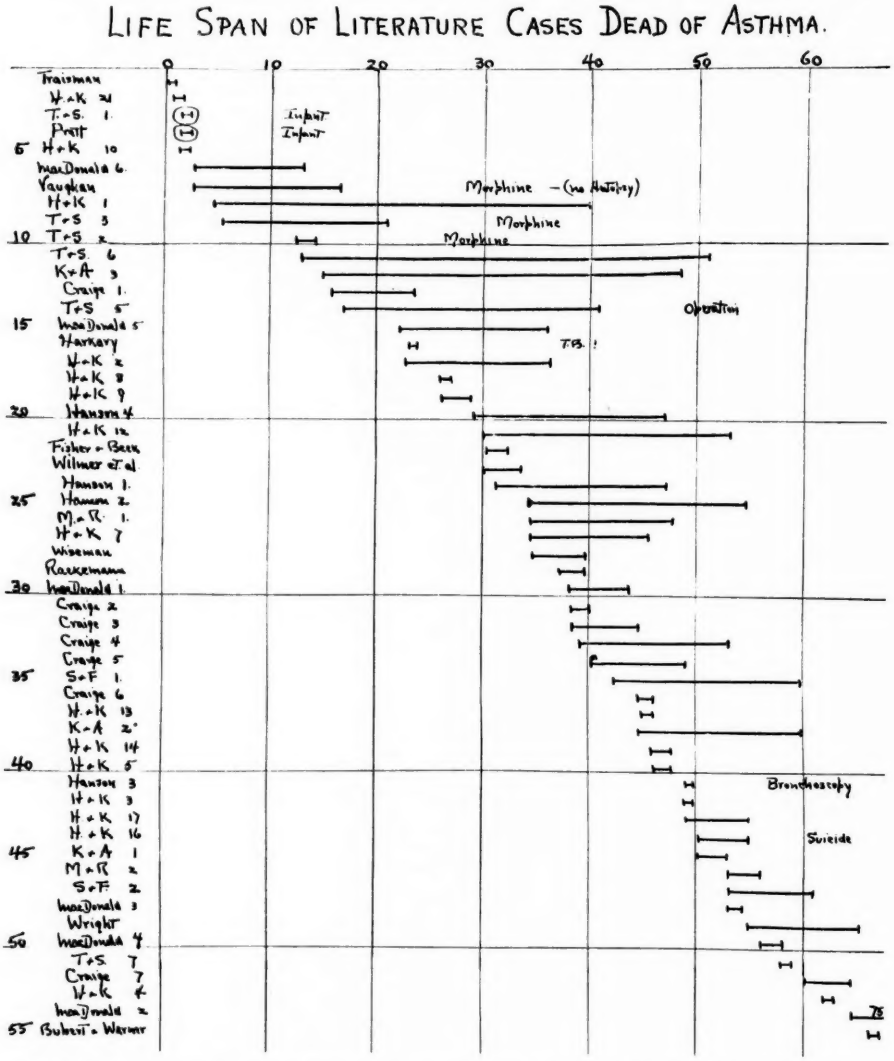

Chart 2.—See legend for Chart 1. Note that all cases in Fig. 2 are *A* cases. Abbreviations in the left-hand column indicate the author and his case number. *H. & K.*, Huber and Koessler;[6] *T. & S.*, Thieme and Sheldon;[8] *K. & A.*, Kountz and Alexander;[13] *M. & R.*, Michael and Rowe;[12] *S. & F.*, Steinberg and Figley.[14]

as has been described by Traisman,[7] by Huber and Koessler,[8] by Thieme and Sheldon,[8] as well as by Pratt.[9]

Deaths in older children from asthma are extremely rare. Macdonald's[10] Case 6, Thieme and Sheldon's Case 2 constitute the only reports. Deaths in young adults occurring between the ages of 20 and 30 are likewise rare. Harkavy's[11] patient showed evidence of tuberculosis as well as of asthma. The others are hard to explain, except that large doses of morphine were given to many of them. As stated above, one wonders whether this treatment could not have made a bad matter worse. Chart 2 includes cases of Michael and Rowe,[12] Kountz and Alexander,[13] Steinberg and Figley,[14] Wilmer, Eiman, and Miller,[15] Hansen,[16] Craige,[17] Wiseman,[18] Fisher and Beck,[19] Bubert and Warner,[20] and Vaughan and Graham.[21]

In the older age group, the cases in the literature are much the same as the cases in our own series. It is quite clear that when asthma begins after age 45, it is possible for the patient to go downhill and die within a relatively short period of time. The reader, however, must recognize that these fatal cases represent only a very small proportion of the total number of persons who develop asthma at the same age and probably under much the same circumstances and yet who are still alive and who can be greatly benefited by proper treatment of their disease.

The importance of Chart 2 is the demonstration that death from asthma is not at all limited to any particular age group, and this in turn should throw a further light upon the classification of the causes of the symptom which is called "asthma."

DISCUSSION

Several questions arise. Does the typical pathology with voluminous lungs and plugged bronchi develop only during the last stages of asthma or are these plugs with the resulting bronchial obstruction characteristic of the whole disease? There are three points which help us. The first is the clinical examination. The chests of patients with asthma are roughly of two kinds. In one the râles are "small" or "fine" and "dry" or "musical." They are evenly distributed throughout both chests, front and back, top and bottom. In the other kind the râles are "larger," or "coarser," and sometimes "moister," but the point is that these coarse râles are not distributed so evenly; they tend to be more numerous in one portion of the chest than in another. Furthermore, this uneven distribution changes, so that after a cough or deep breathing the collection of coarse râles that was in one place will appear to be more marked in another place. Also with the râles goes changes in the intensity of breath sounds which are loud here and diminished there. These two kinds of signs go along with the conception that in some cases asthma depends upon spasm of the bronchial muscles, or perhaps edema of the bronchial wall, whereas in other cases the symptom depends upon mucus in the lumen which can obstruct the flow of

air, and evidently this mucus is not very viscid in that it can move and change to some extent.

The second point derives from certain autopsies. Case 41 of Chart 2 died immediately after bronchoscopy, and Case 44 was a suicide. Quite recently a woman of 50 died during the process of bronchoscopy in the Massachusetts General Hospital. She had had asthma only six months, and in the hospital her asthma continued in severe form without much benefit from treatment. Roentgenograms showed one or two small shadows at the roots of the lungs, and bronchoscopy was advised, partly to exclude the possibility of some local lesion like a bronchial carcinoma, and more because it seemed possible that the procedure would make possible the aspiration of exudate and so relieve her symptoms. The patient was quite apprehensive, but at the time of operation her asthma was not too severe. Preoperatively no morphine was administered. She did however receive nembutal 0.1 Gm. by mouth about one hour before operation. The bronchoscope was inserted in the trachea. At first the breathing was regular enough and all seemed well. Then quite suddenly her breathing and heart beat stopped and she was dead. At autopsy the lungs had a uniform pale gray color and were markedly distended. The larger air passages were quite free of exudate, but cross section of the lungs showed a beautiful picture of sticky material in all the small and middle-sized bronchi. This mucus was sticky and could be pulled out in short strings, but it was not so sticky or tenacious as has been observed in other cases. In each of these patients, death was precipitated by something other than asthma, but it occurred in a patient who was having bad asthma at the time of death. In each case autopsy showed the typical uniform pale gray color with exudate in the bronchi, but it was a thin exudate. Evidently the degree of stickiness, the viscosity of the exudate can vary and change from time to time.

The third point comes from the reports of autopsies made on individuals who died from anaphylactic shock. Sheppe[22] described a man of 30 who died within twenty minutes after a dose of tetanus antitoxin given during treatment of a bullet wound. The lungs were voluminous, but the bronchi did not collapse. Nothing was said in the report about exudate within these bronchi. From the literature Sheppe collected the reports of sixteen such cases. Ten had died after the primary injection, and four after the second injection of foreign serum. Two followed doses of pollen extract. Nine of these sixteen autopsies showed voluminous and distended lungs, but again nothing is said about the presence of plugs.

In 1924 Lamson[23] wrote an important paper in which he collected and reviewed all the literature on cases "whose death may have been due, directly or indirectly, to the protein injected." His Table I shows a total of forty-one cases, but autopsies were reported in only thirteen cases. It is interesting that in these acute cases who died immediately after the injection of foreign protein, no bronchial plugs

were described. The lungs were voluminous but usually dry, and exudate was not especially striking.

The cases of "protracted shock," which Waldbott[24] described in 1934, developed fever, prostration, and tachycardia sometime (2 to 3 days) after the injection of the specific substance in three cases; after contact with a dog in one case and after taking a tablet of sodium salicylate in another; and two small children developed a fever and died shortly after a glass of milk in one case and the drinking of orange juice in the other. The thought that in these cases the bronchial exudate may have produced a complete obstruction with a local collapse favoring the developing of bronchial pneumonia is rather attractive. Fortunately such cases are very unusual.

Wright's[25] patient is included in Chart 2 (Case 49). She had had asthma since the age of 55 and died at the age of 67. Her bronchi were almost completely occluded, but this occlusion was evidently due more to the thickening of the bronchial walls, with infolding of the mucous membrane, than it was to the material in the bronchial lumen. In Wright's case, and no doubt in others, the element of bronchial spasm was evidently quite as important as the element of mucous plugging.

On the whole, it seems reasonable to conclude that the pathology of asthma includes two factors. In the younger group the symptoms depend mostly upon bronchospasm caused usually by absorption of foreign material to which the patient is hypersensitive. The lesion is comparable to that seen in guinea pigs which died in anaphylactic shock, and is sometimes referred to as the "Auer-Lewis lung.[26] It consists chiefly of spasm and perhaps edema, all of which is relieved easily by epinephrine. When, however, the asthma persists over a period of time, then the factor of bronchial exudate comes in. At first this exudate is thin and not too obstructive, but at any time the character of this exudate may change until it becomes so viscid, tenacious, and thick that it occludes the bronchi and suffocates the patient. The mechanism by which this sticky mucus is produced is not yet clear. Whether the goblet cells in the wall of the bronchi can change their form and function under certain conditions is one of the problems in pathology which will be studied later. The possibility of changes in the form and function of the cilia in the larger air passages as recently suggested by Hilding[27] constitutes another problem.

SUMMARY

1. Death from asthma is caused by the development of plugs of tough, sticky mucus which obstruct the bronchi and lead to suffocation.

2. The pathologic picture is typical: it is characterized by voluminous, distended lungs of bluish gray color, and the cut section of which shows all the bronchi, especially those of medium and small size occluded by plugs.

3. Chart 1 shows in graphic form the mode of death and the pathology in fifty of our own cases who died with asthma as the presenting symptom. Of these, 27 showed the pathology which we regard as typical of asthma.

4. Chart 2 shows 55 cases found in the literature which meet the requirements, namely: (a) a clinical history and a mode of death characteristic of asthma, (b) an autopsy showing voluminous lungs and bronchial plugs, and (c) an autopsy showing no gross evidence of other causes of death.

5. This report includes a total of 82 patients who died not only with asthma but because of asthma. Most of these deaths occurred in people whose asthma began after the age of 45, but it is important to note that the typical symptoms and pathology can occur also in younger persons.

REFERENCES

1. Mallory, T. B.: Lecture Unpublished.
2. Rackemann, F. M., and Mallory, T. B.: Intrinsic Asthma, Tr. Am. Clin. & Climatol. A. **57**: 62, 1941.
3. Weille, F. L.: Personal Communication.
4. Sulzberger, M. B., and Simon, F. A.: Arsphenamine Hypersensitiveness in Guinea Pigs, J. ALLERGY **6**: 39, 1934.
5. Rackemann, F. M.: Fatal Asthma. Report of a Case with Autopsy, Boston M. and S. J. **194**: 531, 1926.
6. Huber, H. L., and Koessler, K. K.: The Pathology of Bronchial Asthma, Arch. Int. Med. **30**: 689, 1922.
7. Traisman, A. S.: The Pathology of Asthma in Children, Arch. Pediat. **58**: 407, 1941.
8. Thieme, E. T., and Sheldon, J. M.: A Correlation of the Clinical and Pathologic Findings in Bronchial Asthma, J. ALLERGY **9**: 246, 1938.
9. Pratt, H. N.: The Pathologic Physiology of Bronchial Asthma in Children, New England J. Med. **223**: 626, 1940.
10. Macdonald, I. G.: Local and Constitutional Pathology of Bronchial Asthma, Ann. Int. Med. **6**: 253, 1932.
11. Harkavy, J.: Observations on Fatal Bronchial Asthma, J. ALLERGY **1**: 136, 1930.
12. Michael, P. P., and Rowe, A. H.: Pathology of Two Fatal Cases of Bronchial Asthma, J. ALLERGY **6**: 150, 1935.
13. Kountz, W. B., and Alexander, H. I.: Deaths From Bronchial Asthma: Report of 3 Cases, Arch. Path. **5**: 1003, 1928.
14. Steinberg, B., and Figley, K. D.: Pathology of Asthma, J. LAB. & CLIN. MED. **13**: 921, 1928.
15. Wilmer, H. G., Eiman, J., and Miller, M. M.: Pathologic Picture in a Case of Essential Bronchial Asthma. Roentgen Findings Ante and Post Mortem, J. ALLERGY **7**: 156, 1936.
16. Hansen, O. S.: Death From Asthma, Minnesota Med. **19**: 445, 1936.
17. Craige, B., Jr.: Fatal Bronchial Asthma. Report of Seven Cases, Arch. Int. Med. **67**: 399, 1941.
18. Wiseman, J. R.: Report of a Case of Status Asthmaticus With Autopsy, Ann. Int. Med. **11**: 212, 1937.
19. Fisher, A. M., and Beck, J. P.: Death in Asthma: Case With Necropsy, J. ALLERGY **2**: 149, 1931.
20. Bubert, H. M., and Warner, C. G.: Fatal Asthma. Report of a Case With Bronchial Measurements, J. A. M. A. **104**: 1469, 1935.
21. Vaughan, W. T., and Graham, W. R.: Death From Asthma. A Warning, J. A. M. A. **119**: 556, 1942.
22. Sheppe, W. M.: Fatal Anaphylaxis in Man, J. LAB. & CLIN. MED. **16**: 372, 1931.
23. Lamson, R. W., and Butt, E. M.: Fatal "Asthma," J. A. M. A. **108**: 1843, 1937.
24. Waldbott, G. L.: Allergic Death. VII. Protracted Shock, Arch. Int. Med. **54**: 597, 1934.
25. Wright, C. B.: Death From Bronchial Asthma, J. A. M. A. **94**: 1218, 1930.
26. Auer, J., and Lewis, P. A.: The Physiology of the Immediate Reaction of Anaphylaxis in the Guinea Pig, J. Exper. Med. **12**: 151, 1910.
27. Hilding, A. C.: The Relation of Ciliary Insufficiency to Death From Asthma and Other Respiratory Diseases, Ann. Otol., Rhin. & Laryng. **52**: 5, 1943.

THE VALUE OF THE PATCH TEST IN POISON IVY DERMATITIS, WITH CONSIDERATION OF GROUP REACTIONS BETWEEN RHUS EXTRACT AND TURPENTINE, PYRETHRUM, RAGWEED OIL AND 3-GERANYL CATECHOL

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THE features shown by cases of dermatitis due to plants are often not distinctive enough to permit recognition of the precise cause. Dermatitis due to poison ivy can be recognized usually by the typical linear arrangement of vesicular lesions, but there are instances in which differentiation from dermatitis due to other plants is difficult, if not impossible, by gross inspection. During the summer nearly all instances of acute dermatitis of plant origin are labeled as poison ivy on the basis of probability. It is likely, therefore, that a certain percentage of these diagnoses are erroneous.

The purposes of this communication are twofold: (1) to discuss the value, as well as the limitations, of the patch test in the study of dermatitis from poison ivy; (2) to record data on the incidence of group reactions to turpentine, pyrethrum, ragweed oil, and 3-geranyl catechol in persons hypersensitive to an extract of poison ivy.

The material studied included 72 cases seen chiefly during the summers of 1942 and 1943. Of these, 40 were probable instances of dermatitis due to poison ivy; 26, dermatitis venenata of various other causes, mainly plants; and 6, doubtful examples of poison ivy. With the exception of the second subgroup, all the patients showed positive reactions to an extract of poison ivy. In general, the cases were carefully selected, so that the incidence of 64 per cent positive reactions to rhus extract was probably higher than the figures for normal subjects with the extract used. I was not primarily interested in determining the incidence of positive reactions in the normal population, as this has been done by a number of observers, with essentially similar results.[1] Rather, the intention was to ascertain the diagnostic significance and the general value of this procedure in the study of poison ivy.

The extract* was prepared by extraction of freshly gathered, thoroughly crushed poison ivy leaves and stems with acetone in the proportion of 15 Gm. of vegetation to 250 c.c. of solvent. Eighteen hours later this was filtered, 0.4 per cent phenol added to the filtrate, and finally subjected to bacteriologic filtration with the Seitz filter. The percentage of total solids was not determined. This extract proved to be potent and reliable, even over a period of two years.

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*Material used was prepared by The Endo Products, Richmond Hill, N. Y.

Patch tests were applied in the usual way, generally for two days. In many cases the areas were examined within the next four days, sometimes later. The upper part of the back or the arm was used for testing. Experiments in animals and man indicate that, once hypersensitiveness to *Rhus toxicodendron* is induced, this hypersensitiveness generalizes rapidly over the skin. Shelmire[2] believes that this is always true of sensitization to an external agent and that local hypersensitiveness does not occur. In the case of a potent allergen, such as the active principle in poison ivy, this view is supported by my observations. The occasional report[3] of local hypersensitiveness in poison ivy requires substantiation, although this phenomenon has apparently been demonstrated in various experimental studies and in clinical sensitization by less potent allergens. In my observations, at least, evidence of restricted local hypersensitiveness in dermatitis due to poison ivy has not yet been encountered.

The reactions obtained in patch tests with the rhus extract varied from papular to bullous lesions. In a few instances delayed responses of moderate intensity were observed, these reactions occurring on the third or fourth day. No examples of reactions delayed as long as one or two weeks were encountered in my material. No definite instances of induced sensitization were observed; however, this possibility cannot be eliminated, as I had no opportunity to see these patients several weeks or months later or to retest them. Focal reactions were not observed except in one instance in which the circumstances were unusual (Case 9). No evidence of primary irritation was found. These data indicated that, whereas the extract was potent, it was not too strong. In my material a negative patch test to the rhus extract was considered as eliminating present or past hypersitiveness to poison ivy. Critical observers might argue that some of these cases with negative patch tests represent examples of hypersensitiveness lost over a period of months or years, but my observations lend no support to this view which, in my opinion, is unproved at present in the case of dermatitis from poison ivy.

VALUE OF THE PATCH TEST IN THE STUDY OF POISON IVY DERMATITIS

Many observations show that positive patch tests to a potent extract of poison ivy occur in from 40 to 60 per cent of the normal adult population.[1] These figures are considered as representative of the United States, although variations according to the locality may probably be found. Infants do not react to patch tests with poison ivy extracts when applied for the first time.[4] This, and much other evidence, supports the view that the relatively high incidence of positive patch tests in adults is based on previous contact with, and sensitization by, the plant and, to a lesser degree in the United States, to chemically (and, therefore, immunologically) related plant products.

Hypersensitiveness to poison ivy is therefore one of the few examples of contact dermatitis, in which so large a percentage of the population is affected, and upon this observation rests the chief limitation of this test for diagnosis. My material indicates that in children around the school age a positive test may possibly possess greater diagnostic importance, but exceptions occur.

The figures cited do not signify that all persons showing a positive patch test have had the disease or will acquire it under ordinary conditions of exposure. Instances are encountered which show positive tests with no prior history of dermatitis from the plant and often no recollection of previous contact (Cases 5, 7, and 9). These data are in agreement with the view that the patch test, as usually performed, does not exactly reproduce the actual conditions of exposure.[5] The relation between hypersensitiveness, as shown by the patch test, and the acquisition of clinical manifestations of poison ivy dermatitis depends probably on quantitative factors which are at present difficult to assess. Within limits, the occurrence of clinical disease is a function of the degree of hypersensitiveness and the severity of exposure. Shelmire[2] and Howell[6] have both properly stressed that exposure means direct contact with the bruised plant, and not merely going through fields of poison ivy. Taking all the data into consideration, the following statements seem warranted: (1) Persons showing a positive patch test, but no present or past history of clinical disease, have had a prior sensitizing exposure to poison ivy or possibly to a related plant or plant product; clinical manifestations did not appear either because these persons had no subsequent contact with the plant or, if contact had occurred, the degree of it was mild and the patient only slightly sensitive. (2) The figures based on positive patch tests in the adult population serve only as a general measure of the potential candidates for clinical dermatitis; persons in this group are more apt to get dermatitis from this plant under ordinary conditions of exposure, but even those with negative tests may, in a relatively small percentage of cases, develop the disease subsequently under similar conditions.[7] Among the negative reactors are some who seem fairly refractory to sensitization by poison ivy. (3) In children around the school age a positive test may have greater diagnostic significance, but this is a general rule with exceptions. (4) For a more accurate assessment of these points, quantitative tests based on standardized material, possibly of synthetic origin, must be awaited. Nevertheless, much can be learned from the use of extracts of poison ivy.

Whereas a positive patch test with rhus extract is not of itself diagnostic, a negative result in my material indicated the absence of present or past hypersensitiveness to this plant. This is illustrated by the following representative protocols, in which the diagnosis of poison ivy dermatitis was entertained.

CASE REPORTS

CASE 1.—A woman had a vesicular dermatitis of the face, chiefly on the nose and eyelids. She gave a history of a previous rash that had been diagnosed as poison ivy. A negative patch test with a rhus extract eliminated the diagnosis of poison ivy dermatitis, present and past, despite the history of having contracted the eruption in a park. It was discovered that the present rash had been caused by sunglasses (synthetic plastic) which she wore while golfing in the park, and this was confirmed by a positive patch test and the subsequent clinical course.

CASE 2.—A woman with seasonal hay fever and asthma, probably due to ragweed, complained of swollen red eyelids, the condition having recurred at irregular intervals in the previous few months. The differential diagnosis included dermatitis due to poison ivy, ragweed oil, and nail polish. Patch tests gave negative responses to ragweed oil, pyrethrum, and a rhus extract; the nail polish elicited an intense positive reaction.

CASE 3.—A child, 5 years old, had a typical linear bullous eruption on the right and left arms, and on the thigh. The lesions had been present one month and had become worse a few days before. The diagnosis of poison ivy dermatitis was entertained, and this seemed to be substantiated by a history of a similar attack one year before during the early part of September. Patch tests with a rhus extract, pyrethrum, and ragweed oil were negative. The test was repeated with the rhus extract and again proved negative. It was apparent that the diagnosis of poison ivy dermatitis was incorrect, and so attention was now directed to other possibilities. Finally, it was found that the patient showed intense positive reactions to a fir leaf and stem, and the two attacks could be correlated with exposure to this small tree at home.

The patch test with a rhus extract may occasionally have medicolegal importance. In the following case its use helped to resolve a dispute between two patients.

CASE 4.—Two men came to the clinic, the older one claiming that he had contracted his rash from the younger one. Both worked at the same bench in their business and both had clinical evidence of dermatitis venenata. The young man had noted the dermatitis three days after exposure to poison ivy, the eruption appearing chiefly on the buttocks, and he believed that he had sat in a patch of the plant. Patch test showed an intensely positive reaction to the rhus extract. The older man, who had noted his lesions a few days later, presented a broad band of erythema over the lower part of the back, with swollen eyes and some vesicles between the fingers. This man had never had poison ivy before this, and he claimed that he had handled

the plant many times without ill effects. A patch test with the rhus extract was negative. It was now ascertained that he had visited a camp some days before the rash appeared and had reclined in the grass. Without the patch test, it would have been difficult to resolve this dispute. Had both persons shown positive reactions, no conclusions could have been drawn regarding the relationship between the rashes.

In eight other cases the clinical features were regarded as suspicious for the diagnosis of poison ivy dermatitis. However, this could be eliminated by a negative patch test with rhus extract. These cases show that the diagnosis of rhus dermatitis is made too often during the summer and that the possibility of dermatitis from other plants and weeds should be considered more seriously.

In a number of instances positive patch tests were obtained in patients who presented rashes that were not caused by contact with poison ivy. For example:

CASE 5.—A man, 27 years old, stated that he had never had an attack of poison ivy dermatitis. However, he was not certain about exposure to the plant. His present rash was diagnosed as insect bites. A patch test with rhus extract gave an intensely positive reaction.

This case illustrates the fallacies attendant on drawing conclusions from a positive patch test with rhus extract. It is conceivable that some of the cases with clinical features resembling poison ivy and with positive patch tests to rhus extract may have been caused by other plants due to coincidental prior sensitization by poison ivy. However, this is possible in only a small percentage of cases since especial care was taken in selecting patients with typical clinical features and history.

Some persons believe that they are immune to poison ivy dermatitis. The occurrence of complete immunity to this plant has been denied by some observers because under certain circumstances, as in patching with concentrated extracts, such immunity may be overcome. This can be accomplished in many persons, but there are rare instances in which sensitization cannot be induced even with drastic exposure to concentrated materials capable of producing primary irritation. One of the best examples is that cited by Shelmire,[8] in which such irritative procedures were carried out for eight years without producing sensitization to rhus in this case. In considering this problem it is well to differentiate clinical immunity from what may be called patch test immunity. Two examples will illustrate the point.

CASE 6.—A farmer, 70 years old, had handled poison ivy leaves with bare hands for more than two decades, with no ill effects. During the summer of 1942 he had a dermatitis on the forearm, which was regarded by some as due possibly to poison ivy. A patch test with rhus extract was negative in seventy-two hours and for the next week.

Further study showed that the dermatitis was caused by hypersensitiveness to a tar preparation. Whether this man could have been rendered hypersensitive to poison ivy by applying a more concentrated rhus extract on one or more occasions, I do not know.

CASE 7.—A physician, 39 years old, stated that he had often handled poison ivy and had been covered by it, yet he had never had a clinical attack of the disease. A patch test with rhus extract was negative in forty-eight hours, but the next day a delayed, mild papular reaction appeared. This man was probably mildly sensitive to rhus, the patch test representing a more severe direct contact than the actual conditions of exposure. In this case, the immunity may be considered as relative.

In a few cases prophylactic injections for poison ivy had been given several years previously or shortly before the present attack. Patch tests showed that these persons were still hypersensitive to rhus. As quantitative tests had not been made before and after the injections, it is impossible to know whether the reactions elicited by the patch tests were less intense than previously. However, the occurrence of subsequent attacks and the positive patch tests warrant some scepticism about the alleged value of this treatment. In the following instance the question arose of whether the injection of poison ivy material had been the sensitizing exposure.

CASE 8.—A child, 2½ years old, had an eruption on the trunk one year before observation, while at Peekskill during the summer. This relapsed for about two months but disappeared on return to New York City. The next summer she returned to Peekskill, and subsequently had a recurrence of the dermatitis. This was two weeks before the present observation. Four days later the child was given an injection of poison ivy material.

Examination showed a fine papular rash on the trunk. The right buttock showed a diffuse, bright red eruption. No vesicles or linear lesions were seen, but the details of the dermatosis were obscured by prior application of potassium permanganate solution. A patch test with rhus extract gave an intense bullous reaction.

In view of the atypical features of the eruption, the age of the patient, and the history of two months' duration of the first attack, some observers doubted that the dermatitis had been caused by poison ivy. It was suggested that the child had been sensitized by the injection given ten days before observation. It is true that sensitization is not readily accomplished in man by injection under the skin; however, Strauss[4b] was able to do this in one of ten infants injected subcutaneously. The possibility that the epidermis was contaminated by the injection cannot be eliminated. This case is cited to illustrate the difficulties in evaluating such data.

There are many experimental purposes for which the patch test, or modifications, can be used. Discussion will be restricted to only a few points.

1. Shelmire and Howell determined the intervals between the application of poison ivy material and the success or failure of various, subsequently applied medicaments. These observations raise many points of fundamental interest in regard to the fate of the active ingredient of poison ivy when applied to the skin. Recent work on enzyme systems in relation to catechol and other phenolic bodies[9] may perhaps find application to this important problem. It is interesting that Toyama,[10] in 1918, made a similar suggestion in relation to the dermatitis caused by urushiol.

2. During the summer of 1942, the contents of bullae from positive patch tests to rhus extract were transferred to the same person in several instances. The results given by these fresh patch tests were negative, showing that the active principle was no longer present in the original state. These observations were extended to several other types of contact dermatitis, including that due to paraphenylene diamine, and again the results were negative. These observations substantiate those of White,[11] and Krause and Weidman[12] and the recent studies of Sulzberger and Katz.[13] These data tend to show that the disease is not transferred to other parts of the body by the vesicular lesions in poison ivy dermatitis.

3. According to Keeney,[14] a positive patch test to poison ivy results in a refractory period which persists for two or more months. Unfortunately, the basis for this belief is not fully described in his paper and judgment must therefore be suspended. In discussing this point, Spain[15] stated that he could not confirm this observation. My own results are at variance with the concept of a refractory period, although from time to time observers have claimed its existence in contact dermatitis. In my view the evidence for this is at present scant, and further reports must be awaited.

GROUP REACTIONS TO TURPENTINE, PYRETHRUM, AND RAGWEED OIL

Occasional observers have recorded the occurrence of group reactions to Japanese lacquer (urushiol), *Rhus toxicodendron,* turpentine, and probably other plant oils.[16] From a chemical point of view, it is difficult to discern a relationship between the active principle in poison ivy (probably a catechol derivative) and that in turpentine (in my material mainly α-pinene). However, it is realized that plant products are often closely allied; they may be derived from related parent substances, or may be broken down to similarly configurated compounds. When referring to turpentine, for example, the observer should specify the source, age, concentrations used in testing, and the type of reactions obtained; in one report, at least, it is evident that,

primarily, irritating strengths were used, thus vitiating the conclusions drawn.

In the summer of 1942 it was observed that patients showing positive patch tests to rhus extract often exhibited positive responses to the specimen of turpentine used for routine testing in the concentration of 50 per cent in liquid petrolatum. In a group of twenty-five cases, all of which gave positive reactions to rhus extract, patch tests were made simultaneously with this turpentine, pyrethrum, and ragweed combined oil.* The responses to the extract of poison ivy varied from 3 to 4 plus in this group, except in one instance, a delayed 2 to 3 plus reaction occurring on the third or fourth day.

Of these 25 cases, 23 showed positive reactions to the turpentine, these responses varying from 1 or 2 plus to 3 plus. In two cases the results were negative. These reactions were, therefore, weaker than those shown by the rhus extract, particularly when judged on the basis of relative concentrations. It must be admitted, however, that the diluents used were different, so that comparisons can be made only with reservations. Investigation of the turpentine revealed that it was at least two years old and that it was a specimen of gum turpentine. It seemed reasonable to believe that the high incidence of group reactions to this turpentine might be due to an increase in the phenolic fraction, perhaps due to standing so long with definite exposure to air. I communicated with Dr. S. Palkin, whose fundamental work in this field is well known, but, owing to the war, the unstable phenolic fraction could not be sent to me. However, I was able to obtain pure fresh specimens of various turpentines: gum, oxidized gum (blown), steam-distilled wood, and the sulfate types; also, α-pinene, β-pinene and a tailings fraction. In 7 of the 25 cases these could be compared with the positive reactions produced by the original turpentine. The concentrations were identical in the case of the various turpentines; α-pinene was intentionally applied in a slightly higher relative concentration (50 per cent in liquid petrolatum); β-pinene, 10 per cent in liquid petrolatum; and the tailings fraction, 3 per cent in the same vehicle. In brief, the results showed no correlation between the reactions elicited by the original turpentine and the various specimens furnished by Dr. Palkin. The latter were practically all negative, including α- and β-pinene. These observations show the necessity of evaluating statements referring to so complex and variable a product as turpentine. One point must be mentioned in this regard. The original turpentine had been slowly oxidized over a period of years, whereas the "oxidized" gum turpentine had been air-blown; consequently, although both specimens probably contained an excess of peroxides and other oxidized substances, it could not be concluded that these products were otherwise identical.

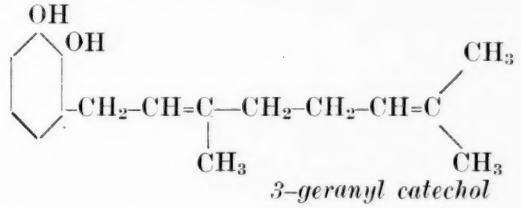
*Lederle Laboratories, Inc.

Of the twenty-five cases positive to the rhus extract, twenty-four gave negative responses to pyrethrum. The single positive, a 1 to 2 plus reaction, may be considered as probably coincidental.

In this same group of twenty-five cases, twenty-two were tested with ragweed combined oil. The results were entirely negative. These data are at variance with the concept which postulates a group relation between poison ivy and ragweed oil. It is possible that a patient hypersensitive to ragweed oil may also give a positive reaction to a rhus extract, but this does not necessarily indicate a relation between the two. Group reactions between pyrethrum and ragweed oil do occur, but a discussion of this point is not relevant to this paper.

GROUP REACTIONS BETWEEN RHUS EXTRACT AND 3-GERANYL CATECHOL

Landsteiner and Jacobs[18] showed in guinea pigs that *Rhus toxicodendron,* urushiol, and geranyl catechol were biologically related. This supports the view that the active ingredient in poison ivy is a catechol derivative with an unsaturated side chain in the 3-position. Geranyl catechol is a catechol derivative with a geranyl nucleus in the 3-position, as shown by the following formula:



3–geranyl catechol

The unsaturated nature of the geranyl nucleus (two double bonds) may be noted.

The results obtained in man substantiated in principle those reported by Landsteiner and Jacobs in guinea pigs. In a group of 24 persons the effects of rhus extract and 3–geranyl catechol could be compared, the latter being applied as a 1 per cent solution in acetone. Intense positive reactions were elicited by both in 18 cases, of which 15 showed more pronounced responses to 3–geranyl catechol.* In 2 of these 18 reactors delayed responses occurred on the third and fourth days, respectively. Of the remaining 6 cases, 4 gave negative responses to both rhus extract and geranyl catechol. In one additional instance there was a delayed papular response to rhus extract, whereas 3–geranyl catechol gave a negative reaction (Case 7). In the last case 3–geranyl catechol elicited a vesicular reaction, the rhus extract a questionable response; however, the rhus patch was loose and further observations could not be made.

*The reactions to 3-geranyl catechol varied from vesicular lesions to various grades of bullous formation with outlying vesicular borders. These appearances were typical of contact dermatitis (eczema) due to hypersensitiveness and were accompanied by various grades of itching. These responses were identical in all respects with those elicited by rhus extract, save for intensity, and, in addition, the features were entirely different from those seen in primary irritation.

These data show the close correspondence between the reactions produced by rhus extract and 3–geranyl catechol. As a rule, group reactions to similar chemicals are weaker than those elicited by the original sensitizer, but this requires comparisons based on identical concentrations in the same vehicle. Since 3–geranyl catechol is an uncommon substance, it is reasonable to assume that the positive reactions produced by it were in the nature of group responses and that their intensity depended on the use of a concentration far in excess of that of the active ingredient in rhus extract. Reference to the method used in making the extract shows that the active ingredient must have been present in a concentration much below 1 per cent in acetone. The close relation between *Rhus toxicodendron* and 3–geranyl catechol is further illustrated by the following case, the only one observed with a focal flare-up.

CASE 9.—A woman, 23 years old, had a contact dermatitis of the lower part of the back, which was traced to the rubber in a new girdle. She had never had an attack of poison ivy dermatitis but was not certain about exposure to the plant. On two separate occasions within a week she showed delayed positive reactions to 3–geranyl catechol applied as patches to the back and left arm, respectively, these reactions reaching their height as vesicular itchy areas. Some two weeks later she was tested with rhus extract applied to the right arm. About twelve hours later focal flare-ups with renewed itching occurred at both sites of 3–geranyl catechol. The response to rhus extract was intensely positive. The ability of rhus extract to produce so striking a flare-up in this case provided, in my view, biologic evidence of a close chemical relation between the active ingredient in rhus and 3–geranyl catechol. My interpretation of the focal flare-up was that it was specific in the sense that it was elicited by the application of a chemically related substance. I have not encountered, thus far, any example of nonspecific flare-up which was so strikingly localized as in this case.

In the following instance patch tests were made with corresponding concentrations of related chemical substances, the results indicating that the reaction to 3–geranyl catechol was based not on the geranyl nucleus alone, but probably on its combination with the catechol configuration.

CASE 10.—A boy, 10 years old, had a first attack of poison ivy dermatitis, which was contracted in a camp. Patch tests showed a 3 plus vesicular reaction to rhus extract, and a 3 to 4 plus response to 3–geranyl catechol. Two days later the following substances were tested, each in a 1 per cent solution in acetone: citral, geraniol, geranyl acetate, citronellal, citronellol, and hydroxycitronellol. All gave negative results, and the same was true of isoprene in both 50 per cent and 25 per cent concentrations in liquid petrolatum.

SUMMARY

1. The results of my studies support the following more or less generally accepted opinions on the uses and limitations of the patch test in relation to poison ivy dermatitis:

a. Diagnostic: A positive patch test with a potent rhus extract does not prove the presence of dermatitis due to poison ivy, but simply indicates sensitization to the plant, past or present. The diagnostic value of the test is depreciated by the high incidence of positive reactions in the normal adult population. Perhaps greater diagnostic significance can be attributed to a positive test in children below the school age, but this general rule has exceptions. In my view a negative patch test eliminates past and present hypersensitiveness to *Rhus toxicodendron*; upon this point rests the chief value of the test in differential diagnosis of dermatitis due to poison ivy. No substantial evidence has been published, thus far, to indicate that a negative patch test occurs in persons who have become spontaneously or otherwise desensitized months or years after the attack of poison ivy dermatitis.

b. Therapeutic: The quantitative patch test is an important method of checking the value of treatment in this disease.

c. Prognostic: A positive patch test does not necessarily mean that the patient has had clinical dermatitis from poison ivy or will acquire it under ordinary conditions of exposure. The relation between the results obtained with the patch test and the acquisition of clinical disease depends probably on quantitative factors involving the degree of hypersensitiveness and the severity of exposure. Those showing positive patch tests are more apt to acquire a dermatitis from contact with rhus under ordinary conditions than those with negative patch tests, but the rule is not invariable; a relatively small number of adults in the United States who show negative patch tests may also subsequently develop hypersensitiveness to poison ivy with a clinical attack. A distinction should be made between immunity as indicated by a negative patch test and immunity as revealed by contact with the plant under ordinary conditions of exposure. There are apparently rare instances in which the most drastic methods of sensitizing the skin have failed to produce hypersensitiveness to poison ivy.

d. Experimental: The value of the patch test in experimental studies cannot be overstressed.

2. Evidence is presented to show that there is no apparent biologic relation between hypersensitiveness to poison ivy and that to fresh turpentines of various types or to α- and β-pinene. Group reactions may be encountered with old specimens of turpentine, and it is assumed, although proof is lacking, that this may have been due to an increase in the phenolic fraction of turpentine. This problem needs further study.

3. Evidence of a group relation between the active ingredient in poison ivy and pyrethrum or ragweed oil was not found.

4. Evidence is presented to show, in substantiation of the work of Landsteiner and Jacobs in guinea pigs, that, in man, 3–geranyl catechol is biologically related to the active principle in poison ivy. Hypersensitiveness to 3–geranyl catechol seems to be dependent on the unsaturated geranyl group in combination with the catechol configuration.

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REFERENCES

1. Spain, W. C.: Studies in Specific Hypersensitiveness. VI. Dermatitis Venenata, J. Immunol. **7**: 179, 1922.
   a. Knowles, F. C., Decker, H. B., Pratt, A. G., and Clarke, J. A.: Susceptibility of Allergic and Nonallergic Persons to Rhus Toxicodendron, Arch. Dermat. & Syph. **38**: 773, 1938.
   b. Keeney, E. L., Sunday, S., Gay, L. N., and Lynch, K.: Poison Ivy Dermatitis. I. The Diagnostic Value of the Patch Test Made With an Ether Extract From Fresh Leaves and Stems of the Poison Ivy Plant, Bull. Johns Hopkins Hosp. **69**: 482, 1941.
2. Shelmire, B.: Contact Dermatitis From Weeds: Patch Testing With Their Oleoresin, J. A. M. A. **113**: 1085, 1939.
3. Field, H., and Sulzberger, M. B.: Experiments in Poison Ivy Sensitivity, J. ALLERGY **7**: 138, 1936.
4. Coca, A. F.: Studies in Specific Hypersensitiveness. VII. The Age Incidence of Serum Disease and of Dermatitis Venenata as Compared With That of Normal Allergies, J. Immunol. **7**: 193, 1922.
   a. Strauss, H. W.: Experimental Study of the Etiology of Dermatitis Venenata, J. ALLERGY **5**: 568, 1934.
   b. Strauss, H. W.: Artificial Sensitization of Infants, J. ALLERGY **2**: 137, 1931.
5. Sulzberger, Marion B.: Dermatologic Allergy, Springfield, 1940, Charles C Thomas.
6. Howell, J. B.: Evaluation of Measures in Prevention of Ivy Dermatitis, Arch. Dermat. & Syph. **48**: 373, 1943.
7. Greenberg, S., and Mallozzi, E. D.: Experiments in Poison Ivy Sensitivity: Effects of Specific Injections on the Level of Sensitivity to Quantitative Patch Tests and on Clinical Susceptibility, Arch. Dermat. & Syph. **42**: 295, 1940.
8. Shelmire, B.: The Poison Ivy Plant and Its Oleoresin, J. Invest. Dermat. **4**: 337, 1941.
9. Nelson, J. M., and Dawson, C. R.: Tyrosinase, Advances in Enzymology, vol. 4, 1944 (In press).
10. Toyama, I.: Rhus Dermatitis, J. Cut. Dis. **36**: 157, 1918.
11. White, J. C.: Dermatitis Venenata, Boston, 1887, Cupples and Hurd.
12. Krause, G. L., and Weidman, F. D.: Ivy Poisoning, Preventative Treatment, With Special Reference to the Element of Individual Susceptibility, J. A. M. A. **84**: 1996, 1925.
13. Sulzberger, M. B., and Katz, J. H.: The Absence of Skin Irritants in the Contents of Vesicles, U. S. Nav. M. Bull. **41**: 1258, 1943.
14. Keeney, E. L.: Studies on Human Hypersensitivity to the Poison Ivy Plant, J. ALLERGY **12**: 599, 1941.
15. Spain, W. C.: Discussion in reference 14.
16. Goldman, L., and Pfosi, H.: Patch Tests With Lacquers, J. ALLERGY **6**: 579, 1935.
17. Tuft, L.: Clinical Allergy, Philadelphia, 1937, W. B. Saunders Company.
18. Landsteiner, K., and Jacobs, J.: Studies on the Sensitization of Animals With Simple Chemical Compounds, J. Exper. Med. **64**: 625, 1936.

PENICILLIN ALLERGY

On the Probability of Allergic Reactions in Fungus-Sensitive Individuals

Preliminary Experiments*

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With the advent of almost every new drug, particularly if it is used parenterally, there have arisen problems concerning allergic manifestations. Usually reports on allergic reactions from a particular drug, or precautionary limitations relative to its use, have not appeared until such a therapeutic substance has been widely used. Penicillin, one of the newest and most generally discussed drugs, has thus far had restricted use because of its limited output and regulations placed on its distribution. It will not be long before penicillin, and perhaps similar antibiotic agents, will be available for more general use. It would be far better to have a broad idea of the probabilities of allergic manifestations from this drug before it is released to the medical profession as a whole.

Reactions analogous to serum sickness have been described.[1] These have been mainly urticaria and have appeared in 5.7 per cent of those receiving penicillin in the series reported. Such reactions have occurred on the initial or subsequent administrations; the period of sensitization has been temporary and it has been possible to proceed with therapy in spite of these reactions. Whatever the explanation of these phenomena, they in no way resemble the classical and severe allergic reactions which would be likely to follow the injection of an allergen to which the individual had been naturally sensitive. The question that presents itself is: How likely is one to have allergic reactions from penicillin because he is sensitive to the Penicillium spores commonly present in the air?

Bernstein and the author[2] have shown that Penicillium spores constitute 11 per cent of the fungus spore content of the air in midwestern United States. Since, from the author's experience,[3] about 20 per cent of allergic patients in the same area are sensitive to fungi and about 30 per cent of the latter react to Penicillium, approximately 6 per cent of allergic persons are sensitive to the antigen of the Penicillium family. Indeed, the first authentic demonstration of mold sensitivity was an experiment conducted by Blackley,[4] in about 1865, in which he pro-

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voked an attack of hay fever and asthma in himself by inhaling the spores of *Penicillium glaucum* from a pure culture of the mold. We have repeatedly shown, both in connection with species of Penicillia and other fungi, that species specificity is not to be expected. Those sensitive to one Penicillium have reacted to other species of this genus. In connection with the experiments recorded here (Table I), it was clearly shown that *Penicillium notatum* is no exception to this rule. It may be argued, of course, that the chemical nature of penicillin and its low molecular weight would make it unlikely that it would contain the original antigen. This argument might be considered valid if it were not for the fact that at the present time only 10 to 20 per cent of the commercial product is penicillin; the remainder constitutes impurities, which may presumably contain some of the antigen.

SKIN TESTS AND RESULTS

As a preliminary experiment it was decided to make skin tests with penicillin on Penicillium-sensitive persons. Ten patients who were clinically mold-sensitive and who gave positive reactions with extracts of various Penicillia, such as *P. rubrum* and *P. digitatum*, were chosen for the experiment. All of these subjects also gave positive scratch reactions with extracts of *P. notatum*. Scratch tests with the solid penicillin as well as a freshly prepared solution containing 5,000 units per c.c. were negative. Intracutaneous tests showed that with extracts of all three species positive reactions could be obtained in these patients to dilutions as high as 1:1,000,000 or higher. With the two batches of penicillin which we employed for our tests we had shown that a concentration of 5,000 units per c.c. usually produced false positive reactions in normal controls. In our intracutaneous testing we therefore employed the following concentrations: 5, 50, and 500 units per c.c. Reactions were negative in all cases.

TABLE I

PENICILLIUM-SENSITIVE SUBJECT	P. RUBRUM OR DIGITATUM		P. NOTATUM		PENICILLIN				
	SCRATCH	INTRACUTANEOUS 1 TO 1 MILLION	SCRATCH	INTRACUTANEOUS 1 TO 1 MILLION	SCRATCH WITH SOLID	SCRATCH WITH 5,000 PER C.C.	INTRACUTANEOUS		
							5 μ PER C.C.	50 μ PER C.C.	500 μ PER C.C.
F. S.	++++	+++	+++	++	0	0	0	0	0
J. B.	+	+	++	+	0	0	0	0	0
A. S.	++++	++++	++++	++++	0	0	0	0	0
G. K.	++++	++++	++++	+++	0	0	0	0	0
J. L.	++	++	++	+++	0	0	0	0	0
J. M.	+++	++	+++	++	0	0	0	0	0
L. K.	+++	++	++	++	0	0	0	0	0
Mrs. F.	+	+	+	+	0	0	0	0	0
H. L.	++++	++	++	+++	0	0	0	0	0
G.	+++	++	+++	++	0	0	0	0	0

COMMENT

On first glance the results cited might be interpreted as an indication that Penicillium-sensitive persons are definitely safe from allergic reactions to penicillin. However, certain quantitative factors must be considered. A probably safe dose of the Penicillium extract would be 1,000 times the minimal amount (0.02 c.c. of 1,000) required to give a skin test. On the other hand, a normal daily therapeutic administration of penicillin would be about 200,000 units, or 20,000 times the maximum dose (0.02 c.c. of 500 units per c.c.) used in our tests. This fact, coupled with the greater likelihood of systemic allergic reactions from intravenous administration, makes it impossible to say at the present time that the probability of allergic reactions can be totally ignored. The answer to this question will be more clear when purer and nonirritating penicillin products will be available or when actual therapeutic doses will be administered to Penicillium-sensitive persons. Because also the original source of penicillin is a potent antigen and conceivably at times some of the antigen may be a final contaminant, it is suggested that as an added safeguard every batch of commercial penicillin be tested on known Penicillium-sensitive individuals.

ADDENDUM

Since the above manuscript was written, the author has had opportunity to make tests with more recently prepared penicillin of higher potency (630 units per mg.) and greater purity. A solution containing 25,000 units per c.c. tested intracutaneously gave negative reactions in control subjects and in Penicillium-sensitive individuals. According to these results, this particular preparation could be tolerated by an average Penicillium-sensitive patient in doses of at least 500,000 units.

REFERENCES

1. Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army, J. A. M. A. **123**: 1008, 1943.
2. Bernstein, T. B., and Feinberg, S. M.: Air-Borne Fungus Spores: A Five-Year Survey of Daily Mold Spore Content of Chicago Air, J. ALLERGY **13**: 231, 1942.
3. Feinberg, S. M.: Allergy in Practice, Chicago, 1944, Year Book Publishers.
4. Blackley, C. H.: Hay Fever: Its Causes, Treatment and Effective Prevention, Experimental Researches, London, 1873.

THE IMMUNOLOGIC MANAGEMENT OF A PATIENT WITH ALLERGY

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IN ORDER to understand the immunologic treatment of a patient with allergy, it is necessary to review our concepts of the genesis of such a reaction.

Before an allergic reaction can take place, it is necessary that (1) the body cells be brought in contact with an antigen, and that (2) there be an incubation period for the development of antibodies.

The cells are now capable of reacting when brought in contact with the same antigen. In the clinical allergies this reaction is a wheal which is clinically and pathologically the same no matter what antigen is the reacting substance. For this reason it must be assumed that all of these reactions to plant and animal nonliving antigens are mediated by some common toxic substance which is released from the body cells. This substance has been given the name H-substance by Lewis and Grant,[1] because of its pharmacologic behavior which is indistinguishable from that of histamine. In fact, Dragstedt[2] who has studied allergic reactions extensively states that all of the symptoms of anaphylaxis in the dog can be accounted for by the amount of histamine released during the reaction.

Similarly, Katz and Cohen[3] have shown that blood cells from allergic human beings with hay fever release histamine in vitro on exposure to ragweed antigen, and Katz[4] has even measured its releases from local skin reactions which he produced experimentally in man. None of the workers referred to insist that histamine is the only reactive material present in H-substance, but believe that it plays a dominant role in causing the reaction.

The immunologic treatment of our patient who has already developed antibodies can be directed against: (1) The antibody (reagin), (2) the antigen, or (3) the H-substance.

Studies of experimental anaphylaxis have shown that following a severe but nonfatal shock the animal is refractory and is incapable of reacting to subsequent injections of the antigen for several days. The theoretical explanation for this refractory state is that sufficient antigen was injected to combine with all of the cellular antibodies and that further reaction is impossible until new antibodies are formed. This phenomenon of refractoriness after severe anaphylactic shock was spoken of, therefore, as desensitization.

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Following Noon[5] and Freeman's[6] demonstration in 1911 that increased tolerance to pollens resulted from repeated injections of increasing amounts of pollen antigen with prevention of symptoms in the patient on exposure to the pollen, it was assumed that the mechanism of this result was a desensitization.

This assumption resulted in the term so dear to the heart of the allergist—"desensitization," which is used to describe the procedure followed in the immunologic treatment of patients.

The discovery of the reagin by Prausnitz and Küstner[7] and the elucidation of its properties by Coca and Grove,[8] and Levine and Coca[9] and others lead to a critical examination of this concept. Indeed, it has been shown that instead of finding a reduction in reagin following treatment with its specific pollen antigen, there is either no significant change or a slight increase. The injection treatment of hay fever cannot, therefore, be called desensitization. Neither can it be called hyposensitization for the same reasons. Both of these terms should be dropped in speaking of the injection treatment of allergic patients. One should speak of raising the patients' tolerance, since this is obviously accomplished, and this term does not have any specific connotation as to how the increase is brought about.

Cooke and his co-workers[10] transfused blood from well-treated to untreated ragweed-sensitive patients and found them specifically benefited. Since the blood of the treated patients contained reagin which was added to that already present in the untreated patient, it was obvious that the donor's blood contained some other product which played a part in the result obtained.

Search for this product resulted in the demonstration in the blood of treated patients of a substance which could specifically neutralize ragweed antigen.

Further study of this substance by Loveless[11] and others have demonstrated it to be an antibody which in its physical and chemical properties resembles a precipitin and can be demonstrated as a precipitin by the highly sensitive collodion particle method described by Cannon and Marshall.[12] This antibody, called thermostabile antibody by Loveless, develops in normal human beings and in animals after the injection of ragweed antigen and has the capacity of binding ragweed antigen in vitro so that properly neutralized antigen and thermostabile antibody mixtures give no skin tests in ragweed-sensitive patients and, as pointed out by Hampton, Johnson, Alexander, and Wilson,[13] will no longer react with rabbit anti-ragweed precipitating sera.

Since the discovery of the thermostabile antibody, much work has been done, particularly by Loveless and Cooke and his co-workers, to determine its relationship to the beneficial results in treated ragweed patients. It can be demonstrated in all treated patients. The amount

necessary to protect varies in each patient, but it has been shown by Loveless that approximately the same clinical result is obtained each year if the patient has the same amount of this antibody.

Whether the thermostabile antibody can explain the relief in treated hay fever completely or not is open to discussion. However, it is the only mechanism as yet demonstrable which could explain the results on immunologic principles.

Longitudinal studies of the same patients over several years led Loveless to the conclusion that the responses of human beings to ragweed antigen is like that of the lower animals and men to other antigens.

Animals given a primary series of injections of antigen reach a peak of antibody production after which the curve levels off and does not rise significantly while subsequent treatment is carried out. When an interval of several months is allowed to elapse, the curve of antibody titer in the blood approaches the zero line. If, at that time and for many months thereafter, a relatively small dose of the antigen is administered, a sharp rise of antibody titer results in a very short time. The height of the titer following the booster dose is usually greater than that reached following the initial or primary series of injections.

It seems logical to apply these principles to the management of our hay fever patients as follows:

1. Whenever possible, one should begin treatment of previously untreated cases early enough to give a full course at least four months before the expected date for the season to begin. If this much time is not available, preseasonal treatment should be given.

2. Three weeks before the season, rapid treatments should be begun so as to give 20 to 30 per cent of the amount of antigen administered in the original series of doses before the season starts. The secondary dose is, of course, not to be given to the patients treated preseasonally.

3. Patients who have had treatment in previous years need only the three weeks booster series.

During the past several months we have been working with a ragweed extract which produces good immunity but does not react with reagin and therefore produces no skin test or constitutional reactions. With this material we hope to be able to give the entire primary immunizing treatment in 3 or 4 doses. This would enable us to treat hay fever with 3 or 4 doses the first year, and one dose annually thereafter, if the principles outlined and discussed are sound.

Individual patients differ in their response to antigenic stimulation. Antibody titers, therefore, will vary, and the clinical result following treatment will differ between patients exposed to the same amount of pollen. In addition, individual exposures are never the same. It is not surprising, therefore, that we are satisfied with 80 per cent improvement in any large series of patients.

Once a patient has reached the maximum antibody response of which he is capable, it is useless to continue specific treatment directed toward neutralization of the antigen.

Treatment which effects complete neutralization of the antigen prevents H-substance formation and subsequent reaction. When complete neutralization of antigen is not effected, some H-substance is formed and reaction occurs.

Is there any immunologic method which can attack and neutralize the H-substance which is released?

In April, 1941, Fell reported the preparation of a histamine-azoprotein in which benzylchlor-histamine was conjugated to despeciated horse protein. Immunologic studies in animals demonstrated that this antigen produced antibodies which were specific against histamine. Sheldon, Fell, and their co-workers[14] used the antigen in clinical allergy and made a preliminary report of their findings.

With H. J. Friedman,[15] these studies were repeated and in 1943 we reported that we could produce antibodies against histamine in human beings by the injection of this compound and that certain persons so treated had the capacity to neutralize histamine in vitro as determined by iontophoretic skin tests. Later Fell and his co-workers[16] published their work in detail in the *Journal of Immunology* and demonstrated conclusively that immunized animals displayed a definite resistance to anaphylaxis.

Further observations in human beings have led us to the conclusion that treatment with histamine azoprotein results in a capacity to neutralize histamine in vivo. If histamine represents any part of the H-substance response in allergy, those patietns should be protected against some of the effects of H-substance.

Our clinical impression is that such protection follows treatment, but we all know how difficult it is to evaluate clinical results. We have attempted, therefore, to determine whether treatment with histamine-azoprotein will neutralize H-substance in vivo.

Alexander[17] has studied wheals produced by eserine and has found that these wheals are indistinguishable in appearance and behavior from those produced in allergic reactions. We have used the response of treated and untreated human beings to eserine as a test for the effectiveness of our treatment.[18]

These results demonstrated that immunization against the effects of H-substance is feasible. We have found that the best method of treatment is to give 5.6 c.c. of a solution containing 1 mg. of bound histamine per c.c. in a period of 30 days, using a dosage schedule as follows at five-day intervals: 0.1, 0.5, 1, 1, 1, 1, 1 c.c.

Within two weeks following this series, there will usually be some demonstrable histamine neutralization, but the degree of neutralization

can be increased markedly if a second series of 2.6 c.c. is given at five-day intervals after a rest period of two months.

REFERENCES

1. Lewis, T., and Grant, R. T.: Vascular Reactions of the Skin to Injury (II. The liberation of a histamine-like substance in injured skin; the underlying cause of factitious urticaria and of wheals produced by burning; and observations upon the nervous control of certain skin reactions), Heart **11**: 209, 1924.
2. Dragstedt, C. A.: Anaphylaxis, Physiol. Rev. **21**: 563, 1941.
3. Katz, G., and Cohen, S.: Experimental Evidence for Histamine Release in Allergy, J. A. M. A. **117**: 1782, 1941.
4. Katz, G.: Histamine Release in the Allergic Skin Reaction, Proc. Soc. Exper. Biol. & Med. **49**: 272, 1942.
5. Noon, L.: Prophylactic Inoculation Against Hay Fever, Lancet **1**: 1572, 1911.
6. Freeman, J.: Further Observations on the Treatment of Hay Fever by Hypodermic Inoculations of Pollen Vaccine, Lancet **2**: 814, 1911.
7. Prausnitz, C., and Küstner, H.: Studien über die Ueberemp findlichkeit Centralbl. f. Bakt. **86**: 160, 1921.
8. Coca, A. F., and Grove, E. F.: Studies in Hypersensitiveness. XIII. A Study of the Atopic Reagins, J. Immunology **10**: 445, 1925.
9. Levine, P., and Coca, A. F.: Studies in Hypersensitiveness. XX. A Quantitative Study of the Interaction of Atopic Reagin and Atopen, J. Immunol. **11**: 411, 1926.
10. Cooke, R. A., Barnard, J. H., Hebald, S., and Stul, A.: Serologic Evidence of Immunity With Coexisting Sensitization in a Type of Human Allergy (Hay Fever), J. Exper. Med. **62**: 733, 1935.
11. Loveless, M. H.: Immunological Studies of Pollinosis. IV. The Relationship Between Thermostabile Antibody in the Circulation and Clinical Immunity, J. Immunol. **47**: 165, 1943.
12. Cannon, P. R., and Marshall, C. E.: An Improved Serologic Method for the Determination of the Precipitative Titers of Antisera, J. Immunol. **38**: 365, 1940.
13. Hampton, S., Johnson, C., Alexander, H., and Wilson, K.: Detection of the "Thermostabile" Antibody by Means of the Precipitin Reaction, J. ALLERGY **14**: 227, 1943.
14. Sheldon, J. M., Fell, N., Johnston, J., and Howes, H.: A Clinical Study of Histamine Azoprotein in Allergic Disease (Preliminary Report), J. ALLERGY **13**: 18, 1941.
15. Cohen, M. B., and Friedman, H. J.: Antibodies to Histamine Induced in Human Beings by Histamine Conjugates, J. ALLERGY **14**: 195, 1941.
16. Fell, N., Rodney, G., and Marshall, D.: Histamine-Protein Complexes: Syntheses and Immunologic Investigation. I. Histamine-azoprotein, J. Immunol. **47**: 237, 1943.
17. Alexander, H. L.: Allergic Syndromes in the Absence of Allergens, J. ALLERGY **11**: 163, 1940.
18. Cohen, M. B., and Friedman, H. J.: Immunity Against H. Substance, J. ALLERGY **15**: 245, 1944.

THE SIGNIFICANCE OF ALLERGY IN MILITARY MEDICINE

A Report of the Incidence of Allergic Diseases in a Large Station Hospital, and a Method of Preinduction Evaluation of the Allergic State

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STATISTICS from the Allergy Section of the Station Hospital, Camp, Blanding, Fla., are presented in this report to emphasize the importance of allergic diseases in the military service. A method of preinduction consultation service for the local Armed Forces Induction Station, which has proved an excellent means of eliminating allergic inductees, is also presented.

Statistics on allergic diseases occurring during World War I, except those concerning asthma, are woefully inadequate.[1] Vaughan[2] states: "In 1917 the International Classification of Causes of Diseases did not include allergy." The clinical manifestations of allergy are so multiple that it is only within recent times that it has been incorporated as a definite specialty, and only much later has it come to be recognized as such in military practice.

During the year 1942, 399 patients were admitted to the wards of the Allergy Section, and 911 patients made 2,482 visits to the Allergy Clinic. The apparent ratio of only 2.7 visits for each clinic patient can be explained by the following:

1. Patients with dermatitis venenata, atopic eczema, and contact dermatitis were treated in the Dermatology Clinic.
2. More than half of the total clinic patients were seen during the last three months of 1942 and did not receive desensitization therapy until 1943.
3. There were 143 patients from the Armed Forces Induction Station seen in consultation only once.

The incidence of all allergic diseases has been tabulated in Table I. Asthma comprised 51 per cent of the total number. This is much higher than Blank's[3] recently quoted figure of 15.7 per cent. This hospital's admission rate for asthma of 8.3 per 1,000 approaches the rate of 7.22 per 1,000 hospitalized in World War I, quoted by Vaughan from Medical Department statistics. However, if we correct our rate by subtracting civilian inductees that were admitted for consultation at the request of the Armed Forces Induction Station, we find that our admission rate of soldiers alone was 4.8 per 1,000.

Table II summarizes the disposition of all allergic patients; that is, whether they were returned to full field duty, reclassified for limited service, or discharged for disability. Of all hospital admissions for asthma, 24 per cent were discharged from the service. This represents all disability discharges resulting from allergic diseases, with the ex-

TABLE I

COMPOSITE STATISTICS FOR THE ALLERGY SECTION FROM JAN. 1, 1942 TO DEC. 31, 1942

	CLINIC		WARD		COMBINED	
	ADMISSION RATE PER 1,000	PER CENT OF CASES	ADMISSION RATE PER 1,000	PER CENT OF CASES	ADMISSION RATE PER 1,000	PER CENT OF CASES
Asthma	9.5	39.31	8.30	78.00	18.00	51.22
Hay Fever	3.3	13.83	0.66	5.76	3.90	11.38
Allergic Rhinitis	1.1	4.71	0.10	1.00	1.20	3.59
Atopic Eczema	3.0	12.31	0.16	1.50	3.10	9.00
Contact Dermatitis	0.7	2.91	*	*	0.70	2.06
Dermatitis Venenata	2.5	10.39	*	*	2.50	7.17
Urticaria, Angioneurotic Edema	1.9	8.01	1.22	11.77	3.10	9.16
Migraine	0.2	.69	0.16	1.50	0.30	0.99
G. I. Allergy	0.1	0.33	0	0	0.10	0.15
No Allergic Disease	1.8	7.51	0	0	1.80	5.19
TOTAL	24.3	100.00	10.6	100.00	35.01	100.00

*Cared for on Dermatology Wards, thus not included.

TABLE II

DISPOSITION OF WARD CASES

	TOTAL WARD ADMISSION RATE/ 1,000	DISCHARGED TO FULL DUTY RATE/ 1,000	PER CENT	DISCHARGED TO LIMITED SERVICE RATE/ 1,000	PER CENT	CERTIFICATE OF DISABILITY FOR DISCHARGE (C.D.D.) RATE/ 1,000	PER CENT	INDUCTION STATION CASES RATE/ 1,000	PER CENT
Asthma	8.3	1.17	14.05	1.60	19.16	2.0	23.95	3.52	42.5
Hay Fever	0.6	.34	56.5	0	0	0	0	.26	43.5
Allergic Rhinitis	0.1	.08	75.0	0	0	0	0	.02	25.0
Atopic Eczema	0.16	.16	100.0	0	0	0	0	0	0
Urticaria Ang. Edema	1.22	1.17	91.0	.08	6.8	0.02	2.2	0	0
Migraine	0.16	.16	100.00	0	0	0	0	0	0
TOTAL	10.6	3.1	28.9	1.68	15.8	2.03	19.0	3.82	35.8

ception of one patient with a diagnosis of persistent and incapacitating urticaria and angioneurotic edema. There were 14 per cent returned to full duty and 19.6 per cent reclassified to limited duty. Most of these received desensitization treatment. These figures, when interpreted in the light of therapy, mean that we have been able to successfully rehabilitate as soldiers 58 per cent of our asthmatic patients in the service.

Table III is a tabulation of the length of service in the Army prior to the time of the patient's disability discharge. Our figures show that 65.19 per cent had less than six months' service prior to discharge, and 21.33 per cent had less than thirty days' service. These figures emphasize the importance of special allergy studies prior to induction on all patients with a history of allergy.

To accomplish these studies, the local Armed Forces Induction Station referred inductees to the Allergy Section of the Station Hospital. These patients were hospitalized for three days by authority of Army Regulation 40-505. During this period they received routine studies which consisted of a complete history, physical examination, Kahn test, complete blood count, urinalysis, sputum and nasal smears for eosinophilia, electrocardiogram, x-ray of the chest, and skin tests. These data were evaluated, and the patient's civilian occupation and capacity to carry on were taken into consideration before a final recommendation was made. A complete record of these studies was returned to the Armed Forces Induction Station.

TABLE III

CASES OF ASTHMA, LENGTH OF SERVICE AT THE TIME OF DISCHARGE FOR DISABILITY (C.D.D.)

LENGTH OF SERVICE	C.D.D. RATE PER 1,000	PER CENT
Less than 1 month	.42	21.33
1-2 months	.32	16.00
2-3 months	.24	12.00
3-4 months	.10	5.20
4-5 months	.08	4.00
5-6 months	.13	6.66
Over 6 months to 1 year	.21	10.66
1-2 years	.37	18.66
Over 2 years	.10	5.20
TOTAL	2.00	100.00

A diagnosis of bronchial asthma was made in 132 of the 143 inductees so studied. A recommendation of rejection for military service was made in 42.4 per cent. This rate is approximately double the rate of rejection given in Table II for men in service. These men would have received disability discharges in less than six months if they had been accepted.

War Department mobilization regulations (MR 1-9, dated Oct. 15, 1942) state that bronchial asthma is a disqualifying defect and that a selectee so diagnosed is not acceptable. The degree or severity of asthma is not mentioned in this regulation. On the basis of our clinical experience at this station, we feel that approximately half of these asthmatic patients are capable of either full or limited military service.

The following criteria have been used in determining the disposition of soldiers, as well as candidates for induction:

1. Asthma, bronchial, chronic, perennial, seasonal and mixed.
   A. *Mild.*—When due to inhalants and pollens, especially house dust, full field duty and desensitization in the Allergy Clinic.
   B. *Moderate.*—Reclassification and desensitization if possible.
   C. *Severe.*—Discharged for disability.
2. Asthma, bronchial, infectious (bacterial or intrinsic).
   A. *Mild.*—Full field duty and desensitization with autogenous vaccine.
   B. *Moderate.*—Reclassification and desensitization as in 2A.
   C. *Severe.*—Discharged for disability.

3. Hay Fever, seasonal, chronic (pollinosis).
   A. *Unassociated* with asthmatic manifestations (mild and moderate). Full field duty and preseasonal and coseasonal desensitization therapy.
   B. *Associated* with asthmatic manifestations (severe group). Reclassification and appropriate desensitization therapy, as with 2A.
4. Urticaria. Full field duty with or without histamine desensitization, except for the rare case of chronic urticaria which should be separated from the service (one case given a discharge for disability in 1942).
5. Angioneurotic edema. Same as with 4.
6. Rhinitis, allergic. Full field duty and appropriate desensitization when feasible; also elimination of offending atopen (inhalant or food).
7. Migraine, atopic. Reclassification when proved.
8. Dermatologic allergies. Occasional reclassification or Certificates of Disability for Discharge when of sufficient severity.

DISCUSSION

A high percentage of allergic disease is potentially or actually incapacitating for military service. These conditions are usually chronic and have existed prior to entrance into the military service. Our experience at this station with patients referred by the Armed Forces Induction Station leads us to believe that the universal use of preinduction consultation service will eliminate the needless waste of time and expense in initial training and subsequent disposition of the soldier who is physically incapacitated.

The adoption of a standard detailed criteria for determining disposition would facilitate the handling of these patients, as well as furnish a method of eliminating allergic inductees. Such criteria have been proposed, and in our hands have proved invaluable.

SUMMARY

A statistical analysis of the clinical records of the Allergy Section of the Station Hospital, Camp Blanding, Fla., has been presented.

Asthma was the major allergic problem, representing 51.2 per cent of all allergic diseases.

A preinduction consultation service for the local Armed Forces Induction Station has proved very successful in classifying inductees.

Detailed criteria for evaluating allergic diseases have been given as a guide to disposition.

REFERENCES

1. Crandall, F. G., Jr.: Allergy in Military Medicine, Mil. Surgeon **87**: 337, 1940.
2. Vaughan, W. T.: Problems of Allergy in War Time, Mil. Surgeon **89**: 737, 1941.
3. Blank, P.: Military Aspects of Allergy, J. Lab. & Clin. Med. **28**: 609, 1943.
4. Standards of Physical Examination During Mobilization. Mobilization Regulations, No. 1-9, Section XIII, 58F, p. 24, War Department, Washington, Oct. 15, 1942.

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THE USE OF STRAINED MEATS AS THE PROTEIN BASIS FOR MILK SUBSTITUTES IN THE TREATMENT OF MILK ALLERGY

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IT HAS been pointed out by Hill and Stuart[1] that the only food substances, other than animal milk, providing in suitable concentration all the amino acids specifically needed by an infant for continued normal nutrition are the animal meats and the soybean. Human breast milk would appear to be an ideal preparation for infants sensitive to cow's milk. While it is possible that sensitivity to human breast milk may occur in infancy,[2, 3] such cases are exceedingly rare. The chief difficulties with the use of human breast milk are that it is not always readily available, is not always produced by mothers on the proper diet for a particular allergic infant, and that, when it must be purchased, it is usually quite expensive.

The introduction of a relatively inexpensive and universally available soybean milk by Hill and Stuart[1] in 1929, and the various soybean milks which have been developed have been of tremendous assistance in the care of infants sensitive to cow's milk. However, an occasional infant is found who is also sensitive to soybean milk. These infants are now rare, but with the tremendous increase in the use of the soybean as an article of diet and as a basis for plastics, sensitivity to soybean will surely become more and more common as time passes on. Other substitute milks have been brought forward which for the most part have as their basis carbohydrate foods.[4] The fact that nutritional edema may result from the use of such preparations is illustrated by Case 3 of this article. In infants over 3 months of age who have good appetites and will eat well from a spoon, nutritional deficiencies may easily be made up by the feeding of a variety of semisolid foods. In the case of infants under this age who suffer from allergic manifestations, principally colic, constipation, diarrhea, and eczema, the necessary constituents of the diet are best provided either in solution, or in suspension, in a suitable liquid substitute for milk. There have been many other substitutes for cow's milk which have been used with varying

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success, such as almond and other nut milks and poppy-seed milk.[5] None of these have proved completely satisfactory.

Hydrolized casein[6] should, theoretically, provide a satisfactory milk substitute, at least for short intervals. In my experience, its use has been disappointing. Diarrhea occurs easily with this preparation and milk-sensitive babies do not commonly respond favorably. Perhaps the reason is that infants may be so exquisitely sensitive to milk protein that they will react to it even when present in such minute traces that it cannot be detected by the usual chemical or biologic tests. That the latter is possible is indicated by the work of Ratner and Gruehl[7] and Ratner[8] on so-called allergenically denatured diets. For example Ratner was unable to shock guinea pigs consistently by the injection of Pablum extract and therefore called this cereal mixture a completely denatured food which should be harmless in allergic individuals. However, practically every pediatrician has had experience with infants who developed eczema due to some one of the constituents of Pabium, particularly wheat.

The third class of foods, animal meat, has not been thoroughly studied as to suitability for use in milk substitutes. The use of animal meat in such substitutes is not new. Rowe,[9] in 1931, published formulas using beef and lamb meat juice in milk substitutes. Cohen, Wallace, Mallory, and Rudolph,[10] in 1933, described a milk substitute in which beef is used as the principal source of protein, with other substances added to round out the formula. My personal experience with this preparation has been unfavorable, but it has been successfully used by others and does have a useful place in the armamentarium of the pediatric allergist. The formula contains several substances to which infants are easily sensitized and has the great disadvantage of rigidity. At the author's suggestion, Landau[11] in 1935 prepared and successfully used, in the treatment of eczema, a milk substitute whose basis was thoroughly dried beef muscle from which the fat had been extracted by ether, and the material then ground into a fine powder and rubbed through a fine sieve, similar to the way in which beef is prepared in the powdered form for use in scratch testing. Although we were successful, we were forced to give up this particular method of making a milk substitute because of the time and labor involved. I did not experiment further with meat as the basis for substitute milk until Rowe,[12] in 1941, mentioned homogenized lamb, beef, and beef liver, and suggested their use in such formulas.*

The method of preparation is as follows. The meat is cut into small pieces, and placed in glass-lined kettles to which a small amount of water is added to prevent adhesion of the meat to the kettle. A small amount of salt is added at this point. The meat is then thoroughly, rapidly, and uniformly cooked in an atmosphere of live steam. It is

*These meats were prepared by Harold H. Clapp, Inc., of Rochester, New York, at the suggestion of Dr. Rowe, and under the direction of Dr. Richard A. Reinecke, of the Research Department of that company. These preparations will not be available commercially until after the war.

then passed through a comminuting or straining machine in which a number of blades or paddles are revolving in a cylinder of stainless steel which is perforated throughout, the diameter of each perforation being 1.44 mm. (0.06 inch). The meat is retained in the cylinder and acted upon by the blades until it is sufficiently divided so that it will pass through the 1.44 mm. perforations in the stainless steel cylinder. The meat, when passed through this operation, is technically in a thoroughly homogeneous condition.

The strained meat, together with the broth, is pumped through stainless steel tubing to a glass-lined holding kettle where the product is automatically passed, by stainless steel fillers, into clean, washed jars. The caps are automatically applied to the jars in a tunnel of live steam which replaces the air from the head space, resulting in a highly vacuumized package. The jars are then placed in large steam cookers and sterilized at a temperature of 240° F. In this process the product is rendered completely sterile, making it absolutely safe for use in feeding infants, children, and patients requiring special diets. After completion of the sterilization process, the jars are promptly cooled, and are ready for labeling and casing.

Since these meats are referred to by Rowe[12] as homogenized meats, the question will naturally arise as to whether or not they are homogenized in the sense that milk is homogenized, since that is the one homogenized product with which the pediatrician as well as the public is particularly familiar. In considering this, two different meanings of the phrase "as milk is homogenized" must be considered. In referring to the homogenization of milk, the reference may be directed toward the property of a stable, oil-in-water emulsion producing a completely homogeneous substance. Immediately after the meat is put through the perforated stainless steel cylinder in the manner previously described, it is, technically, thoroughly homogenized. The high temperature of the subsequent sterilization process, however, results in some separation of the fat from the meat, destroying, to a degree, the completely homogenous condition which exists previous to sterilization.

If, in referring to the homogenization of the strained meat as compared with the homogenization of milk, the reference is directed to the particle size in the strained meats, the size of the fat globules in homogenized milk is much smaller than the particle size in the strained meat. In this sense the strained meats cannot be considered to be homogenized in the same sense that milk is homogenized. Therefore it would appear that although these meats in one stage of their process are homogenized from the view point of the food technologist, in the final state they are not, so that it is more accurate to refer to these products as strained or finely divided meats rather than as homogenized meats.

These meats are fine enough so that, when undiluted with water at a temperature of 37.5° C. (100° F.), they will pass through a tube

TABLE I

STRAINED MEATS (ROWE) USED FOR COW'S MILK FORMULA SUBSTITUTES

	WEIGHT (GM.)	MEASURE	CHO	PROTEIN (GM.)	FAT (GM.)	CALORIES	Ca (GM.)	P (GM.)	Fe (GM.)	CL AS NaCL
Strained lamb P—12.23 per cent F—11.17 per cent	270	1⅛ cups	--	33	30	402	0.11	2.07	.015	
Strained beef P—10.74 per cent F—10.07 per cent	307	1¼ cups	--	33	30	402				
Sesame or soy oil	10	2½ tsps.	--	--	10	90				
Sugar (cane or beet)	30	2⅔ tbsp.	30	--	--	120				
Potato starch flour 83 per cent CHO or	24	2⅓ tbsp.	20	--	--	80				
Tapioca flour 88 per cent CHO	23	2⅓ tbsp.	20	--	--	80				
Calcium carbonate 40 per cent Ca	3	1 tsp.	--	--	--	--	1.20	--	--	--
Sodium chloride	1.75	½ tsp.	--	--	--	--	--	--	--	1.75
Water q.s. to 1,000 c.c.		4¼ cups								
TOTAL FOR 1,000 c.c.			50	33	40	692	1.31	2.07	.015	1.75
or for 100 c.c. (per cent)			5	3.3	4.0	69.2	0.13	0.20	.0015	0.175
The above formula compared with Whole cow's milk (Sherman and Bridges)			5	3.3	4.0	69	0.12	0.09	.0002	0.175
Human milk (Bridges)			6.5	1.5	3.3	61.7	0.04	0.01	.0001	0.058

Method of preparation—All measurements are level, using standard measuring cups and spoons. Heat water to boiling in the top of a double boiler. Add sugar, salt, and calcium carbonate. Mix the potato starch or tapioca flour to a paste in 1/3 cup of cold water and stir into the boiling water. Cook for forty-five minutes in a double boiler stirring occasionally to prevent lumping. If necessary, add water to allow for evaporation. Add the strained meat and oil, mix thoroughly and reheat.

Albert H. Rowe, M.D.: To be published.

3 mm. (0.125 inch) in diameter under a hydrostatic head of not more than 5 cm. (2 inches) of the product, provided that the product is stirred to prevent separation of the broth from the more solid portions. This means that they may be fed to patients through a fairly small catheter, a fact which should be of considerable interest to dieticians who must devise for some patients a high protein diet with low bulk. A practical example of this might be for use in feeding cases of jaw injury where it is necessary to keep jaws wired together for any length of time. The meats have also proved extremely useful in the feeding of normal infants.

The formula for the preparation of the milk substitute by using the finely divided or strained meats as a base is shown in Table I, with which Dr. Rowe was kind enough to provide me. I chose lamb as the meat base rather than beef because it has been shown by Ratner and Gruehl[13] that milk can sensitize to bovine serum in experimental animals, and it would be present in the beef muscle. The use of lamb obviates any controversy regarding this question.

From Table I it is evident that such a formula has a wide range of flexibility. Any available animal meat could be used as a basis. Horse meat should be particularly inexpensive and practical for this purpose. Instead of sesame oil, other oils such as corn, olive, etc., could be used. Instead of potato or tapioca flour, many other carbohydrates are available.

One curious effect of the meat milk substitute is that, in the course of four to six weeks' use, the rubber nipples swell to twice their normal size. This is probably due to the action of the fat upon the rubber.

The following three cases are reported as illustrating the successful use of strained meats as the protein basis for milk substitutes in the treatment of milk allergy in infants.

CASE REPORTS

CASE 1.—J. H. L. This boy was first seen at the office, at the age of 9 months, for treatment of eczema. This had started at the age of 3 months, at which time breast nursing, which had been only partial, was completely stopped. Various forms of cow's milk had been employed without relief. He had never been on a milk-free diet. Experience had shown that he could tolerate neither tomato nor Pablum. Environmental control was instituted, and he was placed on a trial diet of soybean milk, taro flour, and crystalline ascorbic acid.

On this regimen, the skin became less oozy and some of the redness disappeared, but the improvement was not striking. Direct testing could not be done because of the universal involvement of the patient's skin. Passive transfer was employed, using both the mother and the father as recipients. All tests were negative. Instead of soybean milk, the boy was then put on the lamb meat milk substitute, using corn oil instead of sesame oil and taro flour (poyo meal) instead of potato

or tapioca starch. Improvement was marked within twenty-four hours and was steadily progressive. When the skin had cleared satisfactorily, it was found by the method of progressive addition of foods that the following agreed with the patient: beet, carrot, chicken (capon), corn, molasses, oatmeal, white potato, Ry-Krisp wafers, and cream of rye cereal. Vitamin C was supplied by means of crystalline ascorbic acid and vitamin D by means of drisdol. These foods were shown to disagree: cow's milk, beef, string bean, soybean, Jello, and pear. Within eight weeks the boy's skin was in almost perfect condition. At the age of 19 months he was successfully and uneventfully vaccinated against smallpox. At the age of 2 years the introduction of milk products, starting with cottage cheese was tried, but had to be discontinued because the eczema recurred.

CASE 2.—D. R. S. This boy was first seen at the age of 4½ months. His eczema apparently started when he was about 1 week old and became progressively worse, despite various changes of cow's milk formulas and goat's milk on which, incidentally, he did worse than on cow's milk. Soybean milk caused slight but not striking improvement. Scratch tests were positive for barley, corn, lactalbumin, oat, pea, and wheat. Egg white gave a delayed positive reaction. At the age of 6 months, in addition to eczema he developed allergic rhinitis as evidenced by the clinical appearance of his nasal mucous membranes and a smear of the nasal secretions which was positive for eosinophiles. At the age of 9 months he had an asthmatic attack. A taro milk formula[14] was tried without relief. He was put on lamb meat milk, and on this he did very well. It was found that he could not tolerate any of the green vegetables, but could tolerate white potato and beet. On this very limited diet plus crystalline ascorbic acid and drisdol he did very nicely and by the time he was 11 months old his skin was quite clear. He was continued on the lamb meat milk until he was about 16 months old at which time he had developed a considerable tolerance for cow's milk and other foods.

CASE 3.—S. L. C. This child was first seen in the Allergy Clinic of Genesee Hospital at the age of 4 months. The child had been breast fed for three weeks and then placed on an evaporated milk formula. Eczema started on the face at that time and soon became severe and generalized. She was admitted to the hospital and direct skin testing with the indicated allergens was negative. She was placed on a diet of Mull-Soy, Drisdol, and crystalline ascorbic acid without relief. Substituting a hydrolized casein mixture for the Mull-Soy did not help and the child developed a severe diarrhea. She was then placed on a taro milk formula[14] and was discharged with a clear skin fourteen days later. It was found that she could tolerate carrots and bananas and ground liver, which was added to increase the protein intake. Three weeks later, she was readmitted because of a severe generalized

edema. The eczema had also recurred because, as was later demonstrated, a cereal containing powdered milk (Cream of Rice) had been added to the diet. The urinary findings and blood chemistry were normal, except that her total serum proteins were 4.2 (normal for age about 6.3) with reversal of the albumin-globulin ratio (albumin 2, globulin 2.2). An analysis of her diet showed that her daily intake of protein had been 20 Gm. whereas the theoretical optimum was 25 Gm. She was put on the meat milks (all of which she tolerated) and made a good recovery. She was discharged on the taro milk plus added protein, because the supply of strained meat for milk was at its end. However, after a few weeks at home, the edema recurred and she is now being kept in the hospital where her serum proteins are being kept up by injections of plasma and she is gradually being taught to eat the less finely ground meats. This is necessary because the child is a poor eater who will not take meats readily unless finely strained as in the meat milk substitutes.

In search of a complete protein food for newborn infants, that is readily available and at least theoretically of a nonallergic nature, it occurred to me that such food might be made by using the human red blood cells now discarded in such large amounts in the processing of plasma for emergency use. Red blood cells consist largely of hemoglobin which is deficient in several essential amino acids and it was my thought that these acids might be added in the process of manufacture of the milk substitute. This problem was suggested to Dr. Earl L. Burbidge,* who felt that this was probably impractical.

Human plasma or serum would probably be suitable for adaptation as protein bases for artificial milks, but at the present time the demands of war preclude their consideration for that purpose. Theoretically, the perfect meat base for an artificial milk would be human muscle tissue.

SUMMARY

1. The use of specially strained meat as a protein basis for milk substitutes in the manner described by Rowe is discussed.

2. Three case reports, illustrative of the successful use of such substitutes, are presented.

REFERENCES

1. Hill, L. W., and Stuart, H. C.: A Soy Bean Food Preparation for Feeding Infants With Milk Idiosyncrasy, J. A. M. A. **93:** 986, 1929.
2. Kerley, C. G.: Allergic Manifestations to Cow's Milk, New York State J. Med. **36:** 1320, 1936.
3. Lombardi, F.: A Case of Probable Idiosyncrasy to Human Milk, Arch. de pediat. de Brasil **14:** 131, 1942. Abstract Am. J. Dis. Child. **67:** 158, 1944.
4. Wolpe, L. Z., and Silverstone, P. C.: A Series of Substitutes for Milk in the Treatment of Allergies, J. Pediat. **21:** 635, 1942.
5. Finkelstein, L. O.: Mohnmilch als Säuglingsnahrung, Ztschr. f. Kinderh. **48:** 552, 1930.

*Associate Director of the Medical Research Division of Sharp & Dohme.

6. Hill, L. W.: Amino Acids as a Source of Nitrogen for Allergic Infants, J. A. M. A. **116**: 2135, 1941.
7. Ratner, B., and Gruehl, H. L.: Anaphylactogenic Properties of Certain Cereal Foods and Breadstuffs, Am. J. Dis. Child. **57**: 739, 1939.
8. Ratner, B.: Definition of Allergenically Denatured Foods, J. Pediat. **16**: 662, 1940.
9. Rowe, A. H.: Food Allergy, Philadelphia, 1931, Lea & Febiger, p. 93.
10. Cohen, M. B., Wallace, B., Mallory, H., and Rudolph, J. A.: A Milk-, Cereal-, and Egg-Free Diet for Allergic Infants, J. Allergy **4**: 395, 1933.
11. Glaser, J., and Landau, D. B.: Unpublished.
12. Rowe, A. H.: Elimination Diets and the Patient's Allergies, Philadelphia, 1940, Lea & Febiger, p. 200.
13. Ratner, B., and Gruehl, H. L.: Anaphylactogenic Properties of Milk, Am. J. Dis. Child. **49**: 287, 1935.
14. Feingold, B. F.: A Vegetable Milk Substitute: Taro, J. Allergy **11**: 488, 1942.

DISCUSSION

DR. BRET RATNER.—Dr. Glaser's attempt to create a substitute for milk in the treatment of the milk allergic case is commendable, for the problem of milk allergy is still regarded as a puzzling one. Many efforts have been made to provide a substitute for this all-important food, which Dr. Glaser has enumerated, but somehow none of them seem to withstand the test of time. The possible explanations for these failures may be considered in three categories: (1) Milk is so uniquely important a food product in childhood, that depriving the child of it for any length of time appears to endanger nutritional balance. (2) Milk is a component of so many foods as to make it difficult to eliminate it entirely from the child's diet. (3) Milk sensitive patients, particularly those suffering from eczema, are usually sensitive not alone to milk but other substances as well. It must be recalled that environmental contacts do play a large role in the infantile eczema case. This last is probably the most important reason for failure with a milk substitute alone.

In my own experience I have found evaporated milk very effective in the treatment of the milk sensitive child. An increasing number of babies are being fed this modification of raw milk, which may be attributed to a recognition of its qualities. The overwhelming majority of babies sensitive to milk are sensitive to the lactalbumin and lactoglobulin fractions. Only a few are sensitive to the casein fraction. Most of these so-called casein cases are exquisitely sensitive to the lactalbumin intimately associated with the casein. In so far as the casein is coagulated in the stomach by pepsin and hydrochloric acid, the only allergens passing the pylorus are the albumin and globulin fractions contained in the whey. Only albumins in a highly soluble form can pass through the intestinal wall and circulate as active allergens. When milk is homogenized and subjected to heat, the albumin fractions become coagulated and cannot, therefore, act as allergens. For this reason in evaporated milk, in which allergens are coagulated, we have an ideal form of allergenically denatured food.

The problem of milk sensitivity, it would seem to me, resolves itself not in seeking new substitutes for milk, but rather into: (a) the judicious use of a heat-denaturized form of milk, of which evaporated milk is an excellent example; (b) the discovery of additional allergenic factors in a case, other than milk sensitivity, and their correction; (c) the treatment of secondary infections superimposed on the original eczema; (d) the correction of existing constitutional dysfunctions, e.g., hypothyroidism.

PRESIDENTIAL ADDRESS

OUR SOCIETY—ITS PAST, PRESENT, AND FUTURE

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FELLOW members of the Society, and honored guests:

The practice of allergy in this country is only about twenty-five years old, but what twenty-five years they have been! The growth of the subject has been amazing. Where, at the beginning, there were a mere handful of men interested in the field, there are today nearly a thousand. Allergy, like Topsy, "just growed." Its growth resembled widely separated amoebae multiplying by sending out pseudopods from each individual cell. The result of this highly individualistic policy made itself immediately apparent in that our specialty became anarchic insofar as any central governing body was concerned. We have had varying schools of thought, each rotating about a central figure, usually in the nearest large medical center, with the result that even today allergists do not speak a common language in terms of standardization of extracts and procedures. Any proposed change was frequently rejected on the grounds of personal hypersensitivity, of which so many of us have been guilty. The future of the subject, its growth and development, was disregarded. The common attitude was to let the future provide for itself. These two decades of indifference reaped their just reward. Organized medicine, of which allergy certainly was a subdivision, regarded us as we were. A bewildering nomenclature, a lack of unanimity even on the simplest matters, bitter differences often based on inconsequentialities, resulted in a specialty virually devoid of stature in the eyes of our medical colleagues. In addition, we permitted the entrance into the field of some men who took the attitude that allergy consisted of needles, syringes, and a patient's extremity; men who failed to appreciate the fact that to know allergy one must first know medicine. Let us face the facts squarely: The want of esteem from which allergy has suffered in the past comes entirely from our own shortcomings.

This lack of confidence in us on the part of our medical confreres reflected itself in the opinion of the lay public, who only began to change their viewpoint after they had been treated by those allergists who were well trained and really knew what they were doing. This lack of public confidence is just beginning to disappear, as a reflection of the improved conditions in our own ranks. Our ability to cooperate, and our capacity to organize and supervise work in allergy, will bring many compensations in the form of esteem on the part of the public and the medical

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profession. The fact that the Army has recognized consultants in allergy indicates that progress has been made. The future of allergy will depend entirely on the vision and unselfishness of this particular group. The indications for the future are clear. There must be unity, there must be standardization, and there must be properly organized and supervised instruction in allergy.

Permit me to review for you certain facts with which some of you are already acquainted:

In 1944 this Society will attain its majority. For, twenty-one years prior to that date, a small group of men met in the office of Dr. Robert Cooke and founded "The Society for the Study of Asthma and Allied Conditions." The purpose of this Society was to further study of asthma and related conditions, and to promote the discussion of the numerous aspects of the subject.

That was the first indication that some of the men in this field recognized these problems from the very beginning. Dr. Cooke was the first of our Society to see that group activity was necesary, and through the years his vision and foresight and devotion to the Society were largely responsible for its growth and development. The presidents who followed in his footsteps firmly established the high traditions which this Society has enjoyed. They were: Drs. Rackemann, Gay, Donnally, Alexander, Clarke, Coca, VanderVeer, Caulfeild, Kern, Hooker, Cohen, Criep, Vaughan, Brown, Huber, Walzer, and Tuft. All of these men have been outstanding leaders and have made important contributions to the subject. All of them have given unselfishly to the field of allergy and still serve as an inspiration for the rest of us.

From the outset, the Society attracted to its membership the best in the field of allergy, and subsequently membership became more difficult to attain. Today full membership is indeed a recognition of the individual's ability as an allergist.

At about the same time there was formed another society, "The American Association for the Study of Allergy." This organization was known as the western society, and ours as the eastern society. In the course of time, membership in both societies became the rule rather than the exception, and in some cases men were elected as president of both societies, with the result that there grew up a sincere feeling of mutual responsibility and esteem. Both organizations were important influences in the field of allergy.

We grew, prospered, and enjoyed an excellent reputation. With its initial nucleus in New York City, the Society attracted to itself the best elements in allergy, in every large city in the eastern part of the United States, and today it is the outstanding Society in the field.

The development of medical specialization had in the meantime become the object of great concern to the entire profession, due largely to the fact that many men with insufficient medical training and back-

ground considered themselves specialists. This was true not only in our subject, but in the entire field of internal medicine. As a result, there was founded the American Board of Internal Medicine, together with the boards of pediatrics, dermatology, otolaryngology, and others. Their function was to outline the requirements for the recognition of specialists in their respective subjects. This marked the end of the peace and serenity of our Society, and from then on many things began to happen.

I am well aware of the criticisms that have been hurled at the entire mechanism of certification, but, in all fairness, let us be objective and examine the record:

When the question of certification in allergy came up for consideration before the Society, there were two schools of thought: One, which was in the minority, felt that the Society should set itself up as a certifying board. The other group, composed of the larger number of members, felt that, in the long run, it would be best to be recognized as a subspecialty of Internal Medicine, and, therefore, believed that certification in allergy should follow certification in Internal Medicine.

There has, however, been considerable criticism on two grounds. The first arose because some of our members were not certified; this was due largely to technicalities of application. I can say frankly to these men that there were errors made, but in organizing anything new, mistakes are unavoidable. I have been told on good authority that efforts are being made to correct these situations wherever possible. It is the duty of the Society to lend its influence and authority to the correction of these errors.

I appreciate the anomalous position of the pediatricians, dermatologists, and otolaryngologists whose practices consist largely of allergy and who have not been certified, and we shall do everything possible to have their boards recognize allergy as a subspecialty. Up to the present time, our efforts have been unsuccessful, but I feel that we should continue our striving in their behalf, and there is no doubt in my mind that eventually this certification will be forthcoming.

Some of our members call for action. What are the possible courses open to us? There are three choices: First, to accept as members of our Society all who qualify and allow certification of allergy to be a matter only for the internist. Second, to establish our own Board of Allergy. This carries with it grave difficulties, not the least of which is the possibility that it may not achieve official recognition. Furthermore, it is imperative to point out that our examinations would have to include internal medicine. Third, to continue as we are, and endeavor to secure for pediatricians, dermatologists, and otolaryngologists recognition as allergists. We offer, have offered, and will continue to offer to cooperate with those boards, as we have with the Board of Internal Medicine. And if it were not for the war, this recognition could be accomplished more readily.

This universal desire for certification recently resulted in the formation of a society which offers independent certification in allergy to its membership. One does not take exception to the formation of a group, or any number of groups, which may be interested in the field, providing their aims and ideals are high. But one can, I believe, take definite exception to a policy of independent certification, since allergy, as I have said before, is and always will be based on medicine, and, to be competent in allergy, one must be well trained in medicine whether it be internal medicine, pediatries, or dermatology. This is the policy that we of this Society and the American Association for the Study of Allergy adopted and have pursued for several years, and which, on the whole, is working well.

For a number of years a merger of the two established national societies interested in allergy has been contemplated, by reason of the fact that their aims and ideals have been identical, and that to a great extent they have enjoyed a mutual membership. Recently, in the belief that this was a propitious time, conversations leading to the consummation of the merger were undertaken, and I am very happy at this time to announce that on Jan. 1, 1944, there will come into being "The American Academy of Allergy," whose membership will consist of the membership and associate membership of both the eastern and the western societies.

This is an important step forward. It eliminates a great many duplications of membership and prevents duplication of activities. Small points of difference may arise in any amalgamation. Let the members of both organizations meet the issue with forbearance and understanding, and I am sure that in a short time we will be, in fact as well as in name, one unified organization. It is the solemn obligation of this newly formed Academy, with its unified strength, to exert itself to the utmost to correct all differences which have arisen in the past. With the prestige that this Academy will possess, no board can refuse justice to our members. The effect of the establishment of this Academy on organized medicine can only be good and must result in a high degree of respect and esteem, provided that we do not remain stagnant and kep our standards high.

I should also like to take this opportunity to thank the various members who served on the committees and worked valiantly in this task. As a matter of record, it might be well to know that our Society was represented by Dr. Spain, Dr. Bullen, and myself, and the Western Society, by Dr. Feinberg, Dr. Cohen, and Dr. Black.

I should like to repeat my thanks to the members of both committees and to state that without the fullest cooperation of the members of the committees of both societies, and at the cost of great personal inconvenience and time, this merger would not have been possible. It necessitated, among other things, a meeting in Chicago, at which time final details were completed.

I have previously given you an account of my stewardship during the past months. Needless to say, the present officers have been very busy taking care of the affairs of the Society.

Now, what of the future? Our organization has one of two choices: It can continue along its present path, strengthened by the larger membership and unity of purpose of this combined group or it can move in new directions.

I believe this newly formed Academy can become the dominant force in the field of allergy, and I should like to present my views as to what its future plans should consist of.

First, let us consider membership. These are to be divided into two classes. One, a full member, to be termed a Fellow; the other to be termed a Member, the equivalent of an associate membership in our present societies. As recognition of their achievements both are to receive a certificate of membership. The Academy will fail to achieve its high purpose, unless each and every member contributes his share. The meetings are to be both regional and national. The national meeting is to be held annually, and whenever possible is to consist of a two-day session.

I believe that the Academy should take an active interest in the teaching of allergy. Let us view the picture as it has existed, and still obtains, with respect to training the future allergist.

The medical student, even under the four-year course, receives comparatively little education in allergy in his undergraduate years. With the advent of the three-year medical course, teaching of allergy has been reduced to a bare minimum, and it should be our first duty to see to it that undergraduate teaching of allergy is increased as soon as the medical curriculum returns to prewar conditions. We have had numerous short graduate courses in the past, the period running from one to two weeks, and these courses are all that have been available to the physician who wished to equip himself to enter this specialty.

Now, I grant that there never could be a single course which would make a man a complete specialist. I believe this to be true, not only in allergy but in every other field. There are lessons to be learned in the hard school of experience that no course can possibly teach. But I feel there is no room for argument when I say that no one- or two-week course could ever possibly equip a man to meet the problems he must face in the practice of allergy as a specialty. What, therefore, is to be done to correct this situation?

In the first place, when this war is over we will have thrust upon us the responsibility of post-graduate teaching of men who have been mustered out of the Medical Corps of the Army. Many of these physicians will want refresher courses, and many will want to become specialists in allergy. I propose that this Academy make plans, now, to do several things. One is to outline in detail the subject matter to be

covered by the various courses to be given. Furthermore, the Society should undertake to publish an approved list of courses and the places and times when these courses are to be given. These should vary from the ordinary refresher course, for the men who have practiced allergy, to the very detailed course for the physician who wishes to become a specialist in any or all phases of the subject. I believe there is a great need for, and that there should be set up, a graduate school in allergy for the physician who wishes to become a specialist.

This should comprise, just as any other school does, elective courses of which the more advanced students could avail themselves. We here in New York have just completed an experiment in education in the field of allergy. The American College of Physicians invited Dr. Cooke to conduct a refresher course. Participating in this were some of the outstanding chiefs of clinics in the city, and, in addition, we had the benefit of Dr. Heilberger in immunology, and Dr. Klemperer in pathology. The success of this composite form of teaching made us feel that there is an excellent chance for this idea to be made general use of. I urge its trial in other centers of the country. The period of such a graduate course could extend from several weeks to several months, and the student could have the opportunity to do practical work in various institutions. Just compare a course in which the student would have open to him all the large clinics in the country, with opportunities for both clinical and investigative work, with the present-day courses. Such a curriculum must prove an enormous stimulus to the subject and will certainly produce excellently trained allergists.

I likewise feel that the field of fellowships should be surveyed, and that there should be made available, at various institutions, under properly recognized teachers, fellowships for training graduate physicians; in addition to American physicians, opportunities for exchange fellows from Latin America should be made available.

The question of publications in the field of allergy should, likewise, receive the consideration of the Academy. We have the JOURNAL OF ALLERGY, The Journal of Immunology, and the new Annals of Allergy, all actively publishing articles in the field of allergy. The Academy should try to make the JOURNAL OF ALLERGY its official organ. I believe there should be an advisory committee to work with the editorial staff to see that changes, wherever necessary, are made. I believe that the JOURNAL should publish, in detail, the proceedings of the meetings of the Academy. I do not, however, feel that we can have an official publication unless our membership pledges to support it, not merely as subscribers, but with contributions.

We should continue a committee on medicaments and pharmaceuticals, whose function will be to aid the government in removing fraudulent preparations from the market and to help evaluate for the membership

all new mechanical devices and pharmaceutical preparations in the field of allergy.

Lastly, may I report that we have established an annual prize for the best scientific paper of the year published in the JOURNAL. We are fortunate in that our Secretary, Dr. Spain, has been generous enough to turn over to the Academy a fund of $1000, representing his salary as Secretary over the past years. The interest of this fund will be the prize which is to be known as the Merits Award. The award will be made annually, for the best paper published in the JOURNAL in any calendar year, and will be open to members as well as Fellows.

I know that this Academy can survive as the pre-eminent organization in allergy in this country only if it gives to the specialty such services as will justify its existence. I likewise feel that we have the brains and the ability in this Academy, and that if we are willing to take a long-range view and interest ourselves completely and unselfishly in the problems outlined, we will always maintain our leadership.

We have taken a step in the right direction, but much remains to be done. Visualize this Academy twenty years from now, actively engaged in educating and training the future allergists. Visualize what it can do to prevent millions from being stolen from the pockets of the public through nostrums and quackery in the form of asthma cures. Imagine the benefits to a patient on going from city to city and finding that each allergist uses similar extracts standardized in the same way. Compare his feeling of confidence and trust with his present-day emotions when he finds each allergist with his own strange extract. Imagine a literature devoid of some of the fancy and whimsy which has been published in our day. Do you not think these are worth striving for? No one expects the realization of all one's dreams and hopes and ambitions in his lifetime. All of us have had to learn the meaning of the word "compromise," but this picture is a possible one, and its realization and fulfillment rest entirely on each one of you.

Before closing, I should like to take this opportunity to convey to you my deep appreciation of the honor that you have bestowed upon me in permitting me to serve as your president for the past year. It has been a privilege for which I thank you sincerely.

Special Reports

ABSORPTION OF POLLEN EXTRACTS FROM THE ALIMENTARY TRACT

Demonstration by Passive Tests

Narcisse F. Thiberge, M.D.
New Orleans, La.

In 1939 I demonstrated that the antigenic power of grass and ragweed pollen was diminished or abolished by artificial gastric digestion, and pointed out that if oral pollen therapy were to be most effective in allergic diseases, it would be better to administer the pollen in enteric coated tablets.

More recently I reported results of oral pollen therapy in fifty-two patients who had asthma, hay fever, and dermatitis due to hypersensitiveness to ragweed or grass pollen. Of these patients thirteen were completely relieved of their symptoms, thirty-seven reported improvement, and fifteen were unimproved.

During these observations, we had noted a reawakening at intervals of a previous skin reaction in allergic patients who were receiving parenteral treatment. These instances were not numerous and appeared only in extremely susceptible subjects. This suggested the idea of ascertaining by the passive transfer test whether or not we could elicit a positive skin response in nonallergic individuals who gave no skin reactions to pollens. We were successful in a limited number of cases. By using the sera of two very sensitive individuals we were able to prove definitely that absorption of pollen extracts occurs through the intestinal wall in sufficient concentration to produce a marked reaction at sites of passive transfer. Although this is not a new observation, the results were so definite that it was felt they should be recorded.

Blood serum was obtained from two individuals, one of whom was known to be hypersensitive to ragweed pollen, the other to timothy pollen. Fourteen healthy medical students, who so far had never suffered from hay fever, asthma, or skin allergy were used for the test. Five one-hundredths of a cubic centimeter of each of the two sera was injected intradermally on the volar aspect of the right arm of each subject, the site of the injections being marked with a dot of silver nitrate solution for future identification. Two weeks later the subjects

From the Department of Medicine, Louisiana State School of Medicine.

were given, by mouth, enteric coated pills, each containing ¼ grain of pollen. Three pills containing ragweed pollen and 3 with timothy pollen were given on a single day. The presence or absence of reaction in the areas of serum injection was noted on the day that the pills were given and results were recorded as positive if definite redness, itching, and whealing occurred, and as negative if no such reaction occurred.

Among the fourteen individuals, so tested, four reacted positively, nine were negative, and one doubtful.

SUMMARY

The sole object of this paper is to demonstrate that under favorable conditions enteric coated capsules of grass and ragweed pollen allow the absorption of unaltered pollen in sufficient concentration to react at sites of passive transfer in nonallergic patients.

NEW TECHNIQUE FOR CUTANEOUS TESTING

Preliminary Report

James Levinton, M.D., Buenos Aires, Argentina

WE believe that this new method will become widely generalized for the following reasons: It is very convenient and economical, much more so than the two procedures now in use for the diagnosis of allergy, i.e., by scarifications and endermal injections. (The cost of syringes, etc., and their sterilization is eliminated.) It saves time, the results are fairly exact (within the limits of similar allergic tests), and, last but not least, it is less painful.

The contamination of the antigens with traces of other antigens in endermal testing is well known as the cause of false positive reactions. This never occurs with the proposed new technique. This new method does not require the employment of adhesive tape or any patch to protect the zone of the skin that has received the allergenic extract. In this it differs from the Vollmer patch test for tuberculin.

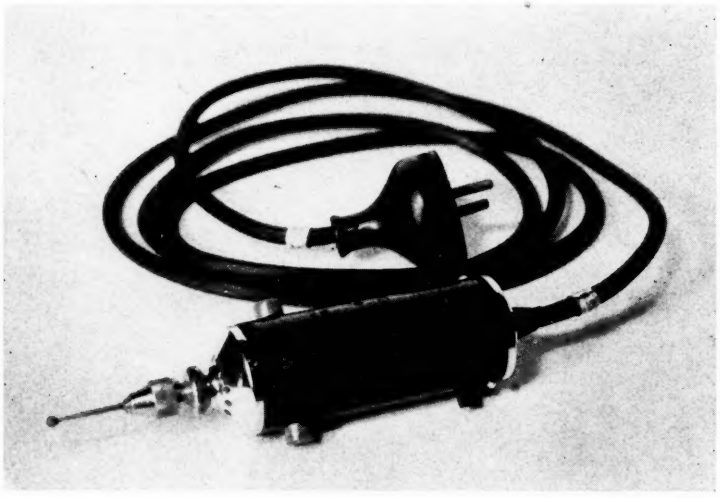

Fig. 1.

The apparatus employed consists of a dental drill mounted on a small portable motor (similar to that used by engravers). The motor makes the drill revolve, which, when applied gently to the skin, causes the epidermic cells to peel. At first, we used the dentist's drill, but this had the inconvenience of not being easy to carry.

The procedure is as follows: The skin of the forearm is cleaned well with a mixture of alcohol and ether. Immediately after, 8 or 10 dots

From the Department of Allergy, Rawson Hospital, Buenos Aires.

are marked with a dermographic pencil, spacing each dot about two centimeters from the other. The apparatus is then applied to the skin in order to peel the epidermic cells by means of slight friction. Then a drop of each extract is placed on the rubbed areas. With practice, each of these frictions is done to an equal depth. The latter is most important, as the friction must be gentle, must not produce any wound, and be just sufficient to let the extract penetrate. After a few trials, one becomes accustomed to making the correct friction. The area becomes shiny at the points that have been rubbed.

The reaction is read twenty minutes after having applied the allergens, observing, as usual, the Lewis' triad.

The development of this technique has been made possible through the generous encouragement of Dr. Alfredo M. Zelasco and the collaboration of Drs. M. Riesel and Pedro Trigos and the staff of the Department of Odontology of the Rawson Hospital: Professor Eduardo Gallego, Drs. A. Ansaldo, M. Benitez, J. Cherteoff, R. Ferro, J. Maresca, and the students Héctor Larre, Raúl Artola, and Ego Etchepare.

Editorial

Nonspecific Inhibition of Anaphylaxis

EVER since the demonstration of the anaphylactic phenomenon, various procedures have been tried in order to define a method which will inhibit, or prevent, anaphylaxis. The attention that was later called to the similarities between allergy and anaphylaxis stimulated the search for such a method, for it was felt that any agent which was found to inhibit anaphylaxis might have a similar salutary effect on allergic processes. It is not our purpose here to discuss the specific methods of antianaphylaxis and desensitization methods in common use in animal and human hypersensitiveness. The search for a method, or an agent, which will be useful in every type of anaphylactic hypersensitivity, no matter what the specific cause, has had considerable attention from many workers, and it is this phase that particularly merits our attention at this time.

The extent of the work on the nonspecific inhibition of anaphylaxis can be surmised from the report of Hill and Martin,[1] who, in 1932, in reviewing the literature on the subject, listed 165 substances, or methods, which had been described in experiments to inhibit anaphylactic shock. These authors listed the following among the agents which have shown evidence of inhibitory action: atropine, barium chloride, barium sulfate, reduction of barometric pressure, chloral hydrate, heparin, benzol in large doses before and during sensitization, intercurrent infection with tuberculosis, sodium bicarbonate, and treatment with one of the antigens in multiple sensitization. The paper is the most complete on the subject and contains a review of all methods published to 1932.

Since that time considerable additional work has been done in this field, but, in most instances, the interpretation of the results is open to question. The common use of potassium salts and sodium thiosulfate in allergic conditions and reactions has prompted Carlson and Whitehead[2] to investigate these substances in experimental animals. Sodium thiosulfate failed to show any protective effect on the anaphylactic reaction. Potassium salts were of value in the prevention of death from the minimal lethal dose of the antigen. Since 25 per cent to 40 per cent of the animals died after 1 minimal lethal dose of the antigen, and higher doses of the antigen were not used, the results cannot be regarded as impressive. Injection of vitamin C (1 mg. per 20 Gm.) thirty minutes prior to the anaphylactic dose reduced anaphylactic mortality in guinea pigs to one-half, according to Hof-

mann.[3] It is interesting to note that inhibition of shock was not present if the animals were kept for twenty-four hours at a temperature of 37° C. Adrenal cortical hormone did not have any inhibiting effect. The same author[4] also observed that veronal, pernocton, and avertin showed reduction in anaphylactic mortality, but the effective dose was either the minimal lethal dose of the drug, or close to it. In both experiments, mice were used. Hiramatsu[5] claimed that vitamin P had a protective effect in anaphylaxis. The available abstract of this article does not contain sufficient details to be convincing. The widely publicized claims for the effectiveness of ethylene disulfonate in allergic conditions led Fisk, Small, and Foord[6] to investigate the action of this substance in animals. They found that ethylene disulfonate did not produce a significant degree of protection against anaphylactic shock. Practically all of the afore-mentioned procedures have been tried in clinical allergy, with very disappointing results.

And now we enter into a more promising phase in the prevention of hypersensitiveness. In 1937, Edblacher and his associates[7] reported that arginine, histidine, and cysteine inhibited or suppressed the histamine contraction of the intestinal strip of guinea pigs. Ackermann and Wasmuth,[8] in 1939, not only confirmed the previous work on arginine but also noted a similar inhibiting effect of the latter on the sensitized intestinal strip. Later, Linneweh[9] claimed that anaphylactic shock could also be prevented in the guinea pig by arginine. The inhibiting effect of histidine on histamine reactions was also noted by Mackay[10] and Halpern.[11] This subject was more recently reinvestigated by Landau and Gay.[12] They confirmed the action of arginine and histidine in preventing the effect of histamine or of an antigen on the intestinal strip of guinea pigs. Death from histamine could be prevented by prior administration of arginine intra-abdominally or intracardially, but all animals had some symptoms of histamine intoxication. The effectiveness of arginine was hampered by the finding that larger doses resulted in a high percentage of fatalities due to the toxic action of the drug. Arginine did not prevent death from anaphylactic shock. The latter observation is particularly informative since it adds evidence to the fact that histamine shock is not the sole mechanism in anaphylaxis. From the clinical standpoint, it is also interesting to note that the authors found that a 2 per cent arginine solution, intracutaneously, failed to produce any effect on the pollen reaction in sensitive subjects, whether given together with the pollen or injected in the wheal.

A still more promising approach to the achievement of the goal of the prevention of anaphylaxis began with the report of Bovet and Staub.[13] These authors showed that the ethylenediamine derivative, thymoxyethyldiethylamine, which they labeled 929F, was capable of preventing histamine and anaphylactic shock in animals. Later, Staub[14] elaborated on her work with 929F and also showed that a related

compound, *N*-phenyl-*N*-ethyl-*N*^{1}-diethylethylenediamine, labeled 1571F, had a similar antihistaminic and antianaphylactic effect. She showed further that neither of these substances affected the skin reaction to histamine. Thymoxyethyldiethylamine was also found by Rosenthal and Brown[15] to prevent anaphylactic and histamine shock in guinea pigs, but the drug is very toxic, since doses large enough to prevent death from more than one minimal lethal dose of histamine, or the antigen, were likely to prove fatal because of drug toxicity. The action of thymoxyethyldiethylamine is apparently specific, since it failed to have an effect on the contractility of acetylcholine, potassium chloride, tyramine, and sodium bicarbonate on the intestinal strip. The ethylenediamine derivative 1571F was the object of further experimentation by Wilcox and Seegal.[16] One to 4 mg. of the drug given prior to histamine administration protected guinea pigs from 2 to 6 minimal lethal doses of histamine, although prostration, cyanosis increased skeletal muscle tonus, and clonic convulsive movements were present. In anaphylactic experiments, 1 to 5 mg. of the drug protected guinea pigs (in seventeen out of twenty-one cases) from death when 2 to 4 minimal lethal doses of the antigen were administered. However, almost all animals displayed shock. In the perfused guinea pig heart, 0.1 mg. of 1571F per liter of perfusion fluid caused an increase in the rate of coronary flow after the addition of histamine. The increased rate and amplitude of the heart beat due to histamine was not prevented by the 1571F. In the hearts of sensitized animals, the drug (5 mg. per liter) prevented the diminution in coronary flow due to the antigen, but the increased rate and amplitude were not prevented. Smaller amounts did not work on the anaphylactic heart. It is apparent that the main action of this drug is to prevent the contraction of smooth muscle.

While it is evident that the experimental search for a method of prevention of anaphylaxis has made considerable progress in recent years it is just as evident that, to date, the available methods are too hazardous to be applied to human allergy. It is not unlikely, however, that continued advancement along the lines indicated above may ultimately result in an effective and safe general method for the prevention of anaphylactic shock and, perhaps, other types of phenomena of hypersensitiveness.

REFERENCES

1. Hill, J. H., and Martin, L.: A Review of Experimental Studies of Non-Specific Inhibition of Anaphylactic Shock, Medicine **11**: 141, 1932.
2. Carlson, R. G., and Whitehead, R. W.: The Effect of Sodium, Potassium and Thiosulfate Ions on Anaphylaxis, J. ALLERGY **14**: 462, 1943.
3. Hofmann, H.: Über die Beeinflussung des anaphylaktischen Schocks durch Vitamin C und Nebennierenrindenhormon, Arch. f. exper. Path. u. Pharmakol. **199**: 631, 1942.
4. Hofmann, H.: Über die pharmakologische Beeinflussung des anaphylaktischen Schocks durch Narkotica und Analeptica, Arch. f. exper. Path. u. Pharmakol. **199**: 664, 1942.

5. Hiramatsu, N.: Studies on Vitamin P (Hesperidin). IV. Influence of Hesperidin Upon Serum Anaphylaxis, Japan. J. Derm. & Urol. **49**: 304, 1941. Abstracted in: Far Eastern Science Bull. **1**: 37, 1941.
6. Fisk, R. T., Small, W. S., and Foord, A. G.: The Experimental Use of Ethylene Disulfonate (Allergosil Brand) in the Prevention of Anaphylaxis in Guinea Pigs, J. ALLERGY **15**: 14, 1944.
7. Edblacher, S., Jucker, P., and Baur, H.: Die Beeinflussung der Darmreaktion des Histamins durch Aminosauren, Hoppe Seyler's Ztschr. f. physiol. Chem. **247**: 63, 1937.
8. Ackermann, D., and Wasmuth, H.: Zur Kentniss der Beziehung des Histamins zum anaphylaktische Schock, Hoppe Seyler's Ztschr. f. physiol. Chem. **260**: 155, 1939.
9. Linneweh, F.: Ueber die Pathogenese und die Grundlagen zur Therapie der Säuglingsintoxication, Monatschr. f. Kinderh. **85**: 215, 1940.
10. Mackay, M.: Effect of Histidine on Histamine Content of Lungs and on Histamine Reactions, Australian J. Exper. Biol. & M. Sc. **16**: 137, 1938.
11. Halpern, B. N.: Action du chlorhydrate d'histidine sur les organes au muscles lisses. Antagonism avec l'histamine, Compt. rend. Soc. de biol. **131**: 509, 1939.
12. Landau, S. W., and Gay, L. N.: Influence of Certain Amino Acids on Histamine Reactions and Anaphylactic Reactions in Intestinal Strip of Guinea Pigs and in Intact Guinea Pigs, Bull. Johns Hopkins Hosp. **74**: 55, 1944.
13. Staub, A. M., and Bovet, D.: Action de la thymoxyéthyldiéthylamine (929 F.) et des éthers phénoliques sur le choc anaphylactique du cabaye, Compt. rend. Soc. de biol. **125**: 818, 1937.
14. Staub, A. M.: Recherches sur quelques bases synthétique antagonistes de l'histamine, Ann. Inst. Pasteur **63**: 400, 1939.
15. Rosenthal, S. R., and Brown, M. L.: Thymoxylethyldiethylamine as an Antagonist of Histamine and of Anaphylactic Reactions, J. Immunol. **38**: 259, 1940.
16. Wilcox, H. B., and Seegal, B. C.: Influence of an Ethylenediamine Derivative on Histamine Intoxication and Anaphylactic Shock in the Intact Guinea Pig and the Isolated Guinea Pig Heart, J. Immunol. **44**: 219, 1942.

—*S. M. F.*

Correspondence

The Editor,

THE JOURNAL OF ALLERGY,

In connection with a series of studies in atmospheric pollen which we are carrying out here at Cardiff, we formed the hypothesis that previous workers had not been justified in assuming for the purpose of calculations based on Stokes' Law that the specific gravity of pollen is unity.

At our request, therefore, Mr. J. W. Fairbairn, B.Sc., of the College of the Pharmaceutical Society, London, kindly determined the specific gravity of a bulk sample of the pollen of timothy grass (*Phleum pratense*), which had been collected in Dr. John Freeman's pollinarium near London. Mr. Fairbairn's figures are as follows:

First Determination:

Wt. of pollen taken = 0.3067 Gm.
Density (by sp. gr. bottle) = 1.138 Gm./c.c.

Second Determination:

Wt. of pollen taken = 0.3298 Gm.
Density (by sp. gr. bottle) = 1.142 Gm./c.c.
Mean value for density = 1.140 Gm./c.c.
The medium used was 95 per cent alcohol.

Mr. Fairbairn described his figures as "exploratory," but they may be taken as giving a substantially accurate estimate of the specific gravity of the air dry pollen. We think that the figure arrived at is so far removed from unity that it would justify the carrying out of a series of such estimations on the collection of bulk specimens which we are in process of forming.

Mr. Durham, however (J. Allergy **14**: 455, 1943), seems to exclude this obvious method of finding the specific gravity of pollen; his method certainly gives quite a different result. Is he able to suggest a reason for the apparent discrepancy?

With your permission, we would like to refer to two other points in Mr. Durham's paper:

1. He states (p. 458) that ragweed granules show no appreciable increase in diameter even when expanded with water, and yet the calculated net volumes of these pollens are greater for "moist" than for "very dry" or "bottle-room" grains. Presumably, the difference is due to the 8 per cent increase noted as the result of the bulk experiments.

2. Mr. Durham's primary determinations of weights of single pollen grains (Table III, p. 459) are evidently those listed under "bottle-room": The "very dry" and "moist" values appear to have been obtained by calculation using the ratios derived from Table I. The values for "moist" should, therefore, be arrived at as shown in Column 2 of our Table A (Column 3 gives Mr. Durham's actual figures).

TABLE A

CALCULATION OF WEIGHTS OF SINGLE POLLEN GRAINS IN MOIST CONDITION

Col. 1	Col. 2	Col. 3
Kind of pollen	Wt. of 1 pollen grain in Gm. $\times 10^{-9}$ (Calculated by us)	Wt. of 1 pollen grain in Gm. $\times 10^{-9}$ (Mr. Durham's figures)
Common Ragweed	$2.02 \times \frac{329}{200} = 3.32$	3.32
Southern Ragweed	$3.07 \times \frac{293}{200} = 4.50$	3.50
Cocklebur	$3.92 \times \frac{347}{201} = 6.73$	6.80

Except for southern ragweed, the results tabulated in Columns 2 and 3 for all practical purposes agree. It would appear, therefore, that for southern ragweed, the correct figure is 4.50: if this is used to calculate the specific gravity, we get 0.65, not 0.51 as in Table III, thus bringing this pollen more into line with common ragweed and cocklebur.

3. Furthermore, in regard to these three pollens, if our reasoning is correct, the "moist" weights need no correction for the 8 per cent volume change (why should they?), and Mr. Durham has given them none. We submit that his statement about the allowance for the 8 per cent expansion (p. 460, line 5) applies not to Table III, but as above suggested to Table II.

H. A. HYDE
National Museum of Wales, Cardiff.
D. A. WILLIAMS
Llandough Hospital, Cardiff.

The Editor,
THE JOURNAL OF ALLERGY,

Dear Sir:

There are two reasons why the determination of specific gravity of pollen grains by the displacement of a measured amount of fluid is difficult or impossible. The first is the extreme absorptive quality of pollen grains, and the second is their solubility in all common liquids. Obviously, if any of the fluid in a pycnometer penetrates the particle being measured, the displacement of fluid cannot be complete. The same is true if any of the substance of the particle is dissolved in the

fluid. Water and alcohol, in different proportions, have been used routinely by allergists in the extraction of pollens for therapeutic use. Hyde has reported that 42.9 per cent of ragweed pollen is soluble in alcohol. Nevertheless, in the course of this study, a reasonable amount of effort was spent in attempting to find a liquid which would neither penetrate nor dissolve pollen granules. Since no such medium was found, and since allergists are familiar with the considerations mentioned above, it seemed hardly worth while to discuss the nonavailability of the pycnometer method in determining pollen densities.

Regarding Hyde's three other points, it is sufficient to say that his assumptions, calculations, and suggestions are correct. The statement beginning on line 5, page 450, should read as follows: "The weights under 'moist' were also calculated from data in Table I. In computing the 'moist' volumes in Table II allowance was made for the per cent expansion of the ragweeds as discussed above, and for Russian thistle as shown in the two different measurements in different media." The determinations which Mr. Fairbairn has made and plans to make may have exploratory value, as he suggests, but it should be noted that they must, in all cases, be too high. Moreover, the degree of discrepancy cannot be constant for all genera and species of pollens because of the different proportion of alcohol extractives in different kinds of pollen. While the timothy figure is necessarily higher than it should be, the error may not be very great because the grass pollens are not nearly so soluble in alcohol as some other kinds.

O. C. DURHAM

Abbott Laboratories
North Chicago, Illinois
May 9, 1944

In Memoriam

WARREN TAYLOR VAUGHAN

WARREN TAYLOR VAUGHAN died suddenly of coronary occlusion at his home in Richmond, Virginia, April 2, 1944. He was 51 years old. He died at the peak of a career which already had many brilliant facets.

He was a scholar. His mind was keen, thirsty, and greedily retentive. His pen was prolific. His *Practice of Allergy* was his best known and most comprehensive book. Others were: *Influenza, An Epidemiologic Study, Allergy and Applied Immunology, Primer of Allergy,* and *Strange Malady.* His contributions to current medical literature were numerous, original, and widely quoted. He was editor-in-chief of *The Journal of Laboratory and Clinical Medicine.* He was, or had been, on the editorial boards of the JOURNAL OF ALLERGY, the *American Journal of Clinical Pathology, American Journal of Syphilis, American Journal of Digestive Diseases and Nutrition,* and *The Folia Clinica Chimica et Microscopica* (Bologne, Italy). He contributed to *The Encyclopedia Americana* and to *Oxford Medicine.* He had received, with pride, an honorary M.S. from his Alma Mater, The University of Michigan.

He was a teacher and a clinician. His talks at local, county, state, and regional medical societies were gems of simplicity and comprehension. The Vaughan-Graham Clinic, which he founded, was a Mecca for the young allergist in search of perfection in the practice of allergy. The continued progress of the Fellows whom he trained in his clinic testifies to the effectiveness of his example and his methods.

He believed in, and was a tireless contributor to, the effectiveness of medical societies. He was an early member of the American Association for the Study of Allergy. As secretary, 1928 to 1938, and President in 1939 he added to the growth and dignity of allergy. He organized and conducted the first Allergy Clinic and Round Table which eventually became the Allergy Section of the Southern Medical Association. He had been President of the Society for the Study of Asthma and Allied Conditions, Vice-President of the Medical Society of Virginia, and Fellow and member of the council of the American Association of the Advancement of Science. He belonged also, to the American Academy of Allergy, the American Medical Association, American Society of Clinical Pathologists, American Rheumatism Association, Society of Investigative Dermatology, and the Virginia Academy of Science. He had honorary memberships in the Institute of Practice of Medicine, Barcelona, Spain, and in the Argentine Society for the Study of Allergy.

He was a patriot. He entered the Army Medical Corps promptly upon completion of his internship at the Peter Bent Brigham Hospital in 1917 as First Lieutenant. By the end of the war he had been promoted to Lieutenant-Colonel and was serving as Chief of Medical Service, Camp Hospital 41, A. E. F. His analysis of the role of allergy as a cause of disability among soldiers and veterans of the last war had much to do with the present policy of not accepting selectees with asthma for duty with the armed forces. From the beginning of World War II until his death, he had been active on The Aerobiology and on the Food Habits Committees of the National Research Council.

He sustained the impetus for accomplishment given to him in his youth by his illustrious father, the late Dr. Victor C. Vaughan, Dean of the School of Medicine at the University of Michigan, and Chairman of the Division of Medical Sciences of the National Research Council. He transmitted this impetus to his four sons, all of whom have brilliant college and medical school records.

He is survived by his widow, Emma Elizabeth Heath Vaughan; by four sons, Dr. Victor C. Vaughan III, Dr. Warren T. Vaughan, Jr., John Heath Vaughan, and David DuPuy Vaughan; and by two brothers, Dr. Henry F. Vaughan, Professor of Public Health and Preventive Medicine at the University of Michigan and Dr. Herbert H. Vaughan, Professor of Romance Languages at the University of California.

His death is mourned by his family, his associates, his patients, his friends, and the many young allergists whom he had befriended.

Oscar Swineford, Jr., Chairman
Leslie Gay
Robert Benson